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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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EAR, NOSE, AND THROAT DEVICES PANEL

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May 1, 2015
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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M E E T I N G

(8:05 a.m.)

DR. WOODSON: Good morning. It's now 8:05 a.m. and I would like to call this meeting of the Ear, Nose, and Throat Devices Panel to order.

I'm Dr. Gayle Woodson, the Chairperson of the Panel. I am a otolaryngologist who retired just at the end of September. I still like to do fun things like this. I was formerly the Professor and Chair of Otolaryngology at Southern Illinois University.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Panel will discuss and make recommendations regarding key issues related to a potential pre- to postmarket shift in clinical data requirements for modifications to cochlear implants in pediatric patients.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation.

Dr. Eydelman.

DR. EYDELMAN: Good morning and welcome, everybody. My name is Malvina Eydelman. I am Director of the Division of Ophthalmic and ENT Devices here at FDA.

DR. HIRSCH: Good morning. My name is Barry Hirsch, and I am a neurotologist from the University of Pittsburgh Medical Center and a professor at the university.

DR. CHANDRASEKHAR: Good morning. I'm Sujana Chandrasekhar. I am a

neurotologist in practice in Manhattan.

DR. HOUSTON: Derek Houston, Associate Professor of Otolaryngology and Philip F. Holton Scholar in the Department -- sorry -- at Indiana University. My expertise is in infant speech perception and word learning.

DR. TOMBLIN: I'm Bruce Tomblin from the University of Iowa. I am now an emeritus professor, and my area is speech language pathology.

DR. BRIETZKE: Good morning. My name is Scott Brietzke. I am from Walter Reed National Military Medical Center in Bethesda, Maryland. I am a pediatric otolaryngologist.

DR. ISHIYAMA: Akira Ishiyama from UCLA, a Professor of Neurotology.

DR. NORTON: Susan Norton, Chief of Pediatric Audiology and Research at Seattle Children's Hospital, and professor at the University of Washington, Department of Otolaryngology, and my area of expertise is pediatric audiology.

LCDR GARCIA: Good morning. Patricio Garcia. I am the Designated Federal Officer for this meeting. Thank you.

DR. TERRIS: Dave Terris, Professor of Otolaryngology at Georgia Regents University in Augusta, Georgia.

DR. KENNA: Marly Kenna. I am a pediatric otolaryngologist with a specialty in otology at Boston Children's Hospital. I'm also a Professor of Otology and Laryngology at Harvard Medical School.

DR. NELSON: I'm Peggy Nelson, Professor of Audiology at the University of Minnesota.

DR. MADELL: Jane Madell. I'm the former Director of the Hearing and Learning

Center and the Cochlear Implant Center at New York Eye and Ear/Beth Israel Medical Center, and I'm now consulting at Pediatric Audiology Consulting.

MS. BROYLES: Hi, I'm Susan Broyles, RN, from Fort Worth, Texas, and also a caregiver of someone with a cochlear implant.

DR. SCOTT: Hi, I'm Cherise Scott. I'm the Consumer Representative. I currently head up the pediatric program at the Global Alliance for TB Drug Development based in New York.

DR. VON JAKO: Good morning. I'm Ron von Jako with GE Healthcare, a surgeon background and research experience in cochlear implants.

DR. WOODSON: Well, welcome to all of you.

If you have not already done so, please sign the attendance sheets that are on the table by the doors.

Lieutenant Commander Garcia, the Designated Federal Officer for the Ear, Nose, and Throat Devices Panel, will now make some introductory remarks.

LCDR GARCIA: Thank you, Dr. Woodson. Good morning, everyone.

The Food and Drug Administration is convening today's meeting of the Ear, Nose, and Throat Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the Industry Representative, all members and consultants of this Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal

ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the purpose of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations regarding key issues related to a potential pre- to postmarket shift in clinical data requirements for modifications to cochlear implants in pediatric patients.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208.

Dr. Ronald von Jako is serving as the Industry Representative, acting on behalf of all related industry. He is employed by GE Healthcare.

The Agency would like to note for the record that Dr. Laurie Eisenberg, who is an invited guest speaker with us today, has acknowledged her professional relationship with the American Academy of Audiology and financial interests in the forms of grants with Advanced Bionics and Cochlear Americas, firms at issue for today's meeting.

The Agency would like to note for the record that Dr. René Gifford, who is an invited guest speaker with us today, has acknowledged financial interests in the form of consulting arrangements and grants with the following firms at issue: Advanced Bionics, Cochlear Americas, and MED-EL.

The Agency would like to note for the record that Dr. Michelle Hughes, who is an invited guest speaker with us today, has acknowledged her professional relationship with the American Academy of Audiology and a financial interest in the form of a contract with MED-EL, a firm at issue.

We would like to remind members and consultants that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Before returning the meeting back to Dr. Woodson, I would like to make a few general announcements.

Transcriptions for today's meeting will be available by Free State Court Reporting, Incorporated.

Information on purchasing videos of today's meeting can be found at the table outside the meeting room.

The press contacts for today are Jennifer Dooren and Deborah Kotz.

All written comments received have been included in the panelists' folders and have been reviewed. A copy of the statements received may be viewed at the registration table.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that all reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Mr. Artair Mallett or AnnMarie Williams. They can be found at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time you speak.

And, finally, please silence your cell phones and other electronic devices at this time.

Thank you very much, Dr. Woodson.

DR. WOODSON: Now we'll hear a presentation from the FDA.

And I'd like to remind the public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

Dr. Peng, please begin.

DR. PENG: Good morning. My name is Shu-Chen Peng, and I am an audiology reviewer in the Division of Ophthalmic and Ear, Nose, and Throat Devices. I'm going to provide an overview on the topics for this Panel meeting: premarket to postmarket shift in clinical data requirements for cochlear implant device approvals in pediatric patients. Dr. Jong Ho Won, Dr. Danica Marinac-Dabic, and I will be presenting on the major topics for today's Panel discussion.

I would like to acknowledge my colleagues, whose names are on this slide, for their input and help to put together the information for this presentation.

In this presentation, I will first give an overview on the purpose of this meeting and provide some background information. Dr. Won will also provide background information on cochlear implant technologies. I will then go over the topics on clinical data considerations, including those that are listed on this slide.

The purpose of this Panel meeting is to seek panelists' scientific opinion on the clinical data requirements to support the premarket approvals for cochlear implant devices in pediatric patients. The Advisory Committee will be asked to discuss and make recommendations on key issues related to the balance of premarket to postmarket data requirements. These issues are categorized into the following three broad categories:

First, device modifications such as technological changes regarding sound processing features and changes to patient characteristics for cochlear implant eligibility that may be suitable for a premarket to postmarket shift for certain data requirements.

Second, appropriate premarket clinical data requirements to support a premarket to

postmarket shift (for example, leveraging clinical data from adults and/or older children).

And, lastly, clinical data study design considerations (for example, study endpoints, test metrics, and subject characteristics) for postmarket data collection to confirm safety and effectiveness and inform future device labeling.

Cochlear implants are implanted electronic hearing devices intended to provide useful sound sensations to patients with a bilateral severe to profound hearing loss, and receive limited benefit from hearing aids, by electrically stimulating nerves inside the cochlear. The device consists of both internal and external components, as shown on this slide. Dr. Won will provide an overview of the device and its technological aspects that are relevant to today's Panel discussion later.

As of December 2012, in the United States, about 96,000 cochlear implants were implanted in patients. This number constituted approximately 30% of all devices implanted in the patients around the world. Also, in the United States, approximately 60% of the cochlear implants were implanted in patients who are 18 years of age or older, while the remaining 40% were implanted in pediatric patients who are 17 years of age and younger. The age cutoff at 18 years is different from the regulatory definition for adult versus pediatric populations, which will be mentioned later in this presentation. Among all devices, approximately 26% were implanted in children aged 5 and younger.

Multi-channel cochlear implants were first approved in the United States in the 1980s, and since then the device technologies have been evolving. There have been three cochlear implant systems being marketed in the United States. These are HiResolution Bionic Ear System, Nucleus Cochlear Implant System, and MED-EL Cochlear Implant System

that were originally approved between 1997 and 2001.

The premarket submissions, or what we call PMA numbers, for these systems and their manufacturers are listed in the table on this slide. Since then, a large number of PMA supplements were approved by the FDA for modifications to these cochlear implant systems, including changes to software and firmware of the external sound processor as well as changes in the implant system hardware.

Testing to support premarket approvals in these PMA supplements included a combination of preclinical testing on biocompatibility, sterilization, electrical stimulation safety, mechanical electromagnetic compatibility, software validation, and clinical testing when necessary and appropriate.

While specific test metrics used to determine clinical performance may differ between adult and pediatric populations, the preclinical testing requirements as well as the requirement for meeting clinical performance data are not different between adult and pediatric patients.

One of our Center's Strategic Priorities (2014-2015) is to strike the right balance between premarket and postmarket data collection. The goal is to assure the appropriate balance between premarket and postmarket data requirements to facilitate and expedite the development and review of medical devices, in particular, high-risk devices of public health importance.

As part of the CDRH Strategic Priorities initiative, the Ear, Nose, and Throat Devices Branch in the Division of Ophthalmic and Ear, Nose, and Throat Devices performed a retrospective analysis for cochlear implants, which are Class III devices and require PMA

approvals. As part of this analysis, the information concerning cochlear implant devices, including their intended use, indications for use, preclinical and clinical performance, and postmarket performance, was reviewed. It was concluded that cochlear implants continue to require PMAs to provide reasonable assurance of their safety and effectiveness.

Also, based on the outcomes of this analysis and in order to facilitate timely pediatric patient access to newer cochlear implant technologies without undermining patient safety, we are proposing shifting premarket clinical data requirements to postmarket for certain device modifications and other changes in the pediatric population.

The regulation authorizes extrapolation of adult data to demonstrate pediatric effectiveness. Section 515A Subpart (b) of the Federal Food, Drug and Cosmetic Act states that "adult data may be used to support a determination of a reasonable assurance of effectiveness in pediatric populations, as appropriate."

Similarly, regarding the subpopulations, the act indicates that the "study may not be needed in each pediatric subpopulation if data from one subpopulation can be extrapolated to another subpopulation."

Even though data extrapolation is a legitimate way to support premarket to postmarket device -- to support premarket device approvals, there are several factors or conditions that would need to be satisfied for data extrapolation being considered appropriate. Details on determining appropriate data extrapolation are described in an FDA draft guidance entitled "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices," published for comments just yesterday, on April 30th, 2015. Since it just came out, this guidance is not available in the Panel pack. But basically, in this

guidance, factors that may prevent or limit data extrapolation are described in detail.

Here we will discuss two relevant factors that may limit data extrapolation to some extent.

First, data extrapolation may be limited to a certain extent if the age difference between the pediatric population or its subpopulation and the available adult data is too large, making it difficult to infer similarity in risk or effectiveness. In such cases, it may be more appropriate to extrapolate to a pediatric age that is closer to the age of the adult population. For example, it might be more appropriate to extrapolate young adult data to an adolescent indication than to a neonate indication.

Second, data extrapolation may be limited to a certain extent if there are important differences between the adult and pediatric populations or pediatric subpopulations, such that the adult data cannot substitute for data from a potential pediatric study to fairly conclude that there is a reasonable assurance of device safety and effectiveness in the pediatric population.

The extent of data extrapolation depends on how the differences are expected to influence potential conclusions of the new study. When data extrapolation becomes inappropriate, the prospective study of pediatric patients may be required.

The Panel will be asked to discuss whether in such cases a study of pediatric patients or a subpopulation of pediatric patients can be conducted as part of a post-approval study, instead of a premarket study, to support the safety and effectiveness of a change to cochlear implant systems.

Device changes to cochlear implants are approved in supplements to the original

PMA. This slide lists a few examples on changes to a speech processor and/or speech-coding strategies approved in PMA supplements.

In one PMA supplement for the HiResolution Bionic Ear System, a new coding strategy called Fidelity 120, designed to enhanced spectral resolution, was approved for adults and pediatric patients aged 5 years or older based on adult clinical data collected under an Investigational Device Exemption, or IDE, application, which will be introduced in a minute.

Another example is the SP12 speech processor, which is capable of delivering stimulation at a higher rate for the Nucleus 24 Cochlear Implant System. It was approved along with several other changes to the device components. The approval was for both adult and pediatric patients based on adult clinical data also collected under an IDE application. Post-approval studies were specifically required to provide confirmatory safety and effectiveness data in both pediatric and adult populations.

The last example is the approval of the Fine Structure Processing, or FSP, coding strategy for the Maestro Cochlear Implant System, which is designed to transmit temporal fine structure information in the low-frequency channels. It was approved with the labeling precaution stating that clinical data were only collected from patients who are postlingually deaf. The approval for the FSP coding strategy was based on the data collected from adult and older pediatric subjects with postlingual onset of deafness, defined as onset of severe to profound sensorineural hearing loss at 6 years of age or older. Unlike the other two examples, the data used to support the premarket approval of the FSP strategy was collected from outside the United States, or OUS studies, which will also be discussed

further in a minute.

As we can see here, for these changes, the requirements of premarket data, post-approval studies, or labeling precaution from adult and/or pediatric subjects appear to vary. Generally speaking, it has to do with the issues and concerns identified for the proposed device change or, more specifically, the uncertainty about the safety and effectiveness for the proposed device change at the time of premarket submission.

In the studies to support premarket approvals of device changes in the examples listed on the previous slide, the study subjects are all able to communicate their perceptual experiences, including speech understanding, to an audiologist performing the test. Clinical data collection from younger children aged 6 and below have not been used to support premarket approvals of device changes, including advances in speech-coding strategies and front-end signal processing features.

For this younger subpopulation it is important to consider the fact that after implantation, it requires additional time for these individuals to fully develop auditory skills and respond to audiologic testing.

Given that longer time requirement for collecting premarket data for pediatric patients at 6 years of age or younger, cochlear implant manufacturers have typically submitted premarket clinical data using adults and children older than 6 years of age. This limitation in premarket clinical data has led to conditions in approved labeling, such as specifying a given device change is only intended for pediatric patients at an older age, such as 6 years of age and older.

On the other hand, there have been plenty of published studies suggesting that

young children can benefit from advances in speech-coding strategies or perform at a level no worse than that with the speech-coding strategy that they currently use.

Meanwhile, FDA is not aware of any serious safety concerns related to the fitting of approved new speech-coding strategies in pediatric patients who are younger in age, such as below 6 years of age.

Keeping these considerations in young children in mind, in the following, Dr. Won will provide an overview on cochlear implant technologies that may be suitable for a premarket to postmarket shift in data requirement. We will then bring up the first set of Panel questions for later discussion.

Dr. Won.

DR. WON: Good morning. My name is Jong Ho Won, and I am a biomedical engineer in the Division of Ophthalmic and Ear, Nose, and Throat Devices. My colleague, Dr. Vasant Dasika, and I prepared this presentation for a brief introduction of cochlear implant technologies that are relevant to today's Panel meeting.

Current cochlear implant systems are composed of external and internal components. For the external components, there is a sound processor which has a battery and at least one microphone. There is also a headpiece which has an antenna coil to transmit power and signals to the internal device through radiofrequency signals. The internal components are surgically implanted. It has a receiver-stimulator placed under the skin and an electrode array which is inserted into the cochlea. For devices that are currently used and marketed in the United States, there are between 12 and 22 electrode contacts on the electrode array.

This block diagram shows a breakdown of cochlear implant processing. There is front-end processing, followed by speech-coding strategy, and finally electrodes deliver pulse-train output to stimulate auditory nerves.

Front-end processing is a set of digital signal processing algorithms that, for example, can help optimize directionality of microphones or improve speech perception in particular situations by reducing background noise.

The speech-coding strategy is a signal-processing algorithm that converts acoustic input into electric signals on individual electrodes.

The figure on this slide shows some of the key design features used in modern speech-coding strategies. In this example, four-channel pulse processing is shown. Acoustic waveforms of input and output are shown below the block diagram. A microphone detects the acoustic sound and then is filtered by bandpass filters. Then you detect envelope components for subband signals typically through activation and low-pass filtering or inverse transformation. These envelope components are then used to amplitude-modulate interleaved -- pulsed, interleaved, fixed-rate, biphasic pulse trains across the electrodes. Finally, patients' auditory nerves are stimulated by amplitude-modulated, biphasic pulse trains. Current cochlear implant systems and current cochlear implant speech-coding strategies are variants of this phasic design.

Over the past 30 years, cochlear implant manufacturers and researchers made significant amount of effort to improve implant hardware and speech-coding strategies. In this chart you see the history of development for three approved cochlear implant manufacturers. As they developed more advanced hardware and newer speech-coding

strategies, speech perception scores in quiet environment situations have gradually improved. We expect further development in these areas by cochlear implant manufacturers and researchers to improve performance in more challenging situations such as noise environments or music perception.

Some examples of technological changes aimed at improving speech perception outcomes for cochlear implants are shown on this slide. To improve spectral resolution of hearing through cochlear implants, efforts have been made to increase the number of physical electrodes, electrode contacts, or use current-steering techniques. In order to improve temporal resolution of hearing, increases in stimulation rates or development of advanced coding strategies to deliver more acoustic temporal fine structure information have been introduced.

Typical examples of front-end processing include beamforming to utilize the directionality of dual microphones, noise reduction such as background noise cancellation or wind noise reduction, and automatic scene analysis to optimize the physical signal processing based on the user's acoustic environment, such as speech conversation in quiet or in noise listening environment.

In consideration of both new speech-coding strategies and front-end speech processing features, we believe that it is important to consider that some young cochlear implant recipients may not be able to accurately report their auditory perceptual experiences with these new strategies and features. Other changes to cochlear implant systems may include enhancements to the programming/mapping software and waterproofing of external sound processor.

When patients receive a cochlear implant, he or she visits an audiology clinic for mapping. In this photo, a child patient is working with an audiologist to map her sound processor. During the programming session, an audiologist assesses -- evaluates implant functions such as electrode impedances, evoked compound action potentials, compliance limits. An audiologist then adjusts mapping parameters such as input dynamic range, speech-coding strategy, front-end processing, and minimal and maximal levels on each electrode.

One example of a new enhancement to the programming software that is currently being investigated is that patients are mapped remotely using telemedicine techniques. While not currently approved in the United States, there are many research efforts by manufacturers and researchers in this area.

In this photo on this slide, an audiologist in a different location from the patient is programming the patient's sound processor by looking at the TV screen and communicating with the patient remotely. For this specific technique, we believe it is important to consider if children can provide reliable subjective feedback during the remote programming, and if the children can pick up the subtle responses to implant stimulation from young children -- if the clinician can pick up the subtle responses to implant stimulation from young children through this configured camera.

Manufacturers have developed various types of waterproof accessories or specifically designed sound processors to enable patients to use their device in various water environments such as during showering or in the pool. For these types of accessories, we believe that it is important to consider usability factors, particularly for the

pediatric population, to evaluate the proper use of these accessories during these activities.

This concludes my presentation. And now Dr. Shu-Chen Peng will continue to present.

DR. PENG: Thank you, Dr. Won, for giving this overview.

With the background information that we have introduced so far, we would like to ask the Panel to discuss the following, that is, if advances in speech-coding strategies for cochlear implants are suitable for the proposed premarket to postmarket shift in clinical data requirements for pediatric patients, particularly those who are younger than 6 years of age.

The Panel will also be asked to also discuss if the following device modifications or changes in indications would also be appropriate for a premarket to postmarket shift in clinical data requirements to support the safety and effectiveness in pediatric patients, particularly those who are younger than 6 years of age.

Device modifications include:

i. Front-end processing of the incoming acoustic signal, such as noise reduction, beamforming, and automatic scene selection;

ii. Enhancements to programming/mapping software; and

iii. Waterproofing of the external processor.

As for changes in indications for use, they include:

i. Severity of sensorineural hearing loss;

ii. Preoperative speech recognition scores;

iii. Asymmetrical hearing loss or single-sided deafness; and

iv. Benefit from bilateral cochlear implantation.

Lastly, the Panel will be asked to discuss any additional changes to the cochlear implant systems or indications that would be appropriate for this premarket to postmarket shift of data requirements for pediatric patients, particularly those who are younger than 6 years of age.

In the next part of this presentation, I will be giving an overview of the clinical data considerations to facilitate Panel discussion. Topics will include current clinical data requirements for premarket approvals, target patient population, supplementary clinical information, and considerations in post-approval studies from a clinical perspective.

Clinical performance data supporting device safety and effectiveness are typically required for cochlear implant premarket approvals as well as for certain device modifications and changes in labeling, including indications for use. These data to support premarket approvals are typically collected under an Investigational Device Exemption or IDE pivotal studies in the United States.

A pivotal study is generally a well-controlled study with adequate study design, including sample size. IDE studies allow an investigational device to be used in a clinical study. These IDE studies are typically prospective, hypothesis-driven studies in which each subject serves as his or her own control and is tested at intervals prior to and following implantation. This within-subject design is used to account for various individual subject factors which can influence the effectiveness outcomes. Studies have clearly described subject eligibility criteria to define a study population with respect to the target age range, severity of hearing loss, and lack of benefit from hearing aids.

The study hypothesis and sample size determination are based on the primary effectiveness endpoint, and typically 50 to 100 subjects are proposed. Study endpoints include both safety and effectiveness endpoints. Device safety is usually determined based on analysis of the number and type of adverse events over the course of the study. Effectiveness endpoints are determined at 6 or 12 months post-implantation, as compared to the performance in the pre-implant best-aided condition.

This slide lists some of the common test metrics, including speech recognition tests and patient-reported outcomes, used to determine device effectiveness in clinical studies used to support premarket approvals for cochlear implants for both adult and pediatric populations.

Speech recognitions are used to measure a patient's ability to recognize speech sounds, words, or sentences. In a speech recognition test, the patient typically has to repeat a word or a sentence that is presented via a loudspeaker or point to a word or a picture that corresponds to what he or she perceives. The response is calculated in percent correct. These test metrics vary in aspects such as test condition, that is, in quiet versus in noise, availability of contextual cues, and lexical familiarity, and thus vary in their difficulty levels.

When test metrics are used, it is important to know the age appropriateness for the tests, particularly for pediatric patients at a relatively younger age. In fact, all speech recognition tests listed on this slide require a subject's ability to perform a speech recognition test and may not be suitable for kids at a younger age, such as below 6 years of age.

In addition to speech recognition tests, patient-reported outcomes, or PRO, are also commonly used to support labeling claims for improved quality of life in adult patients, or changes in a child's ability to perceive sounds as reported by parents. With this type of test metric, the patient is asked to respond to questions on various domains, including perceived disability and quality of life with the device or device features on, as compared to the best-aided condition or with the device feature off.

For younger pediatric patients who may not properly be assessed using speech recognition tests, parent-reported scales, including the IT-MAIS and MAIS, listed on this slide are often adopted. These two parent-reported scales are structured parent interview tools designed to assess the child's spontaneous response to sound in his or her own everyday listening environment.

It is important to note that the patient-reported outcomes have their limitations when adopted in any clinical studies to determine device effectiveness to support premarket approvals on cochlear implants or their device changes.

The limitations are primarily related to the fact that it is not feasible to blind subjects to treatment and the fact that a control group does not exist in most of these clinical studies, given the within-subject design of the study.

The Panel will be asked to address questions related to test metrics used in the pediatric patients, particularly those at a relatively young age who may not be able to respond to speech recognition tests, and performance has to be determined on patient-reported outcomes such as IT-MAIS and MAIS.

This slide lists the FDA's definition for the pediatric patient population and how they

can be divided into several subpopulations. Pediatric patients refer to those individuals who are 21 years of age or younger. They can be divided into four ranges of subpopulations, including:

- Newborn (neonate) from birth to 1 month of age;
- Infant, greater than 1 month to 2 years of age;
- Child, greater than 2 to 12 years of age; and
- Adolescent, greater than 12 through 21 years of age.

We can see here that age 21 is adopted to define the upper age limit for the pediatric population, but note that this upper limit does vary among experts. This adoption is consistent with the definition found in several sources in the regulations and is considered useful for some medical devices and their clinical trials. However, in the clinical studies supporting premarket approvals for cochlear implants and their device changes, the cutoff age between adult and pediatric populations is 18 years. There has not been a consistent way to divide pediatric patients into subpopulations based on the chronological age.

In fact, among the pediatric patients who receive a cochlear implant, additional characteristics should also be taken into consideration when clinical performance is assessed. Some of these common subject characteristics include, but are not limited to, disease condition (for example, onset of deafness), severity of the sensorineural hearing loss, etiology, activity/maturity level, and anatomical/physiological differences compared to the adult population and among pediatric subpopulation.

This slide compares the pediatric subpopulations for cochlear implantation at a

younger versus older age. This cutoff, although somewhat arbitrary, is adopted here based on the onset of deafness being pre- versus postlingual, which also implies if the child has had prior hearing and spoken language experience prior to implantation. Cochlear implantation in pediatric patients at younger ages may pose challenges in how device effectiveness is determined in this subpopulation. This is because many of these younger children are either born deaf or become profoundly deaf before ages 5 or 6.

After receiving a cochlear implant, it would take several years for these individuals to develop auditory skills and mastery in their spoken language. Given their limited ability to report their auditory perception experience as well as test for speech recognition, it may not be feasible to determine if a given device change in technology, such as a new speech-coding strategy, provides benefits as intended or how it compares to the existing one.

On the contrary, the pediatric patients who receive a cochlear implant at a relatively older age are often those who are postlingually deaf, that is, become profoundly deaf after developing some language, typically after ages 5 or 6. Determination of cochlear implant effectiveness in these individuals is not so different from that in the adult population.

When compared to those at a young age, these older children tend to be more mature in many aspects of development, yet their neuroplasticity may tend to be relatively lower. Those children at a relatively young age, in contrast, are less mature in all aspects of development, yet they may have high levels of neuroplasticity. Given all of their patient characteristics, it is not surprising to see the difference in the test metrics for each subpopulation, as well as in the time it requires to determine device effectiveness between the two subpopulations. This comparison highlights the importance of considering patient-

related factors such as chronological age, onset of deafness, and so on, when we discuss issues related to a proposed premarket to postmarket shift in clinical data requirements for the pediatric patient population.

Cochlear implants are currently approved for use in patients age 12 months and older in the U.S. market. Popular studies in the literature have consistently established the long-term effectiveness for cochlear implants in pediatric patients of whom devices are indicated for. Generally, they benefit from the device use, as shown in their long-term speech and language outcomes, even though individual variability in outcomes exists.

To account for the observed individual variability, several patient factors, including age at implantation and length of device use, have been identified as consistent predictors for post-implant speech and language outcomes among pediatric users. More specifically, better outcomes are typically associated with a shorter duration of deafness, younger age at implantation, and longer device experience.

Currently, for device modifications to cochlear implants, clinical data from adult patients have not typically been considered to be sufficient to support indications, especially for pediatric patients who are younger than 6 years of age, for a variety of reasons. For example, the pediatric population exhibits subject characteristics that are quite different from the adult population, for example, onset of deafness being pre- versus postlingual.

In most cases, when only premarket adult data are used to support approval, FDA has required specific labeling to allow pediatric use, for example, under adult supervision or used only by those who are able to report discomfort and device-related problems. Ideally,

clinical data that adequately addresses each targeted pediatric population should be obtained to support a pediatric indication. However, it may be possible to demonstrate a reasonable assurance of device safety and effectiveness by extrapolating from adult to pediatric or from one pediatric subpopulation to another. In such cases, it is important that justifications are given to support what data can be extrapolated in a certain way.

Given the patient and device characteristics among cochlear implant recipients, including adult and pediatric populations, the Panel will be asked to discuss the following:

a. If data from adult clinical trials are suitable for extrapolation for the premarket approval of advances in cochlear implant technologies in older pediatric populations (e.g., age 6 and above).
b. The type of premarket clinical data (e.g., adult, older children) that may be suitable to support a premarket to postmarket shift in clinical data requirements for approvals.
c. Specific considerations that need to be addressed when using adult or older pediatric subpopulation data to support safety and effectiveness in younger pediatric patients (e.g., age at implantation, developmental and cognitive factors, prelingual or postlingual onset of severe to profound deafness, severity of the sensorineural hearing loss, and etiology).

In addition to performance data gathered in pivotal studies under an IDE, there are other sources of scientific evidence that are considered valid to support reasonable assurance of device safety and effectiveness, for example, published literature and OUS data, that is, data gathered from outside the United States. Premarket approvals for

cochlear implants have always relied on the results from pivotal studies under IDEs, even though additional sources of data, primarily published literature and OUS data, have also been used as supplementary information to support reasonable assurance of device safety and effectiveness.

For device modifications, in addition to data from IDE studies being used as the primary source of evidence in PMA supplements, published literature and OUS data have also been provided as the primary supporting evidence to establish device safety and effectiveness. Even though premarket approvals can be supported using published reports or OUS data, it is important to note that the evidence required for establishing reasonable assurance of device safety and effectiveness depends on factors associated with the patient and device characteristics.

Given the inherent heterogeneity of the patient populations for cochlear implants and certain device characteristics (for example, it is usually not feasible to blind study subjects with device turned on/off or without device modifications), it is important that study information is included in sufficient detail when published reports and/or OUS data are adopted to support device safety and effectiveness.

Literature reports are one source of valid scientific evidence. Note, however, they have certain limitations when used as the only or primary source for supporting device premarket approvals. Here we list two major limitations. First, publication bias, which may occur when studies with positive findings are more likely to be published than those without positive findings. In addition, the likelihood of studies with significant results reported in the literature is much higher than those with insignificant findings. One other

limitation is that the literature reports may lack a sufficient description on aspects such as the clinical study plan, study conduct, subject accountability, and missing data handling. Such a limitation often limits FDA's ability to identify and assess any potential bias and determine any impact of such bias on study findings.

Also, it is often not feasible to identify deviations from prospectively planned statistical analysis. Literature reports are often susceptible to post hoc analysis issues, that is, analyses that are performed after the data have been looked at for any hypotheses that were not pre-specified.

Issues related to multiplicity in statistical testing are not consistently addressed in these reports. For example, multiple testing may be conducted for different subgroups or factors, such as time points or test metrics, without any statistical adjustments for controlling for the Type I error rate.

Another evidence source, OUS data, also have been used to support premarket approvals of device modifications. OUS data can be used to support premarket approvals if the data are adequate, ethically derived, and scientifically valid. To utilize OUS data, it is critical to establish that the study patient population in the OUS study is relevant to the target population in the United States and can be properly evaluated for the proposed device intended use.

To this end, any possible differences in clinical conditions in the U.S. versus OUS populations should be addressed. Similarly, study populations in the U.S. versus OUS studies may be different due to cultural, educational, and language backgrounds. These aspects all need to be addressed or justified as comparable.

For cochlear implant recipients, test metrics administered to determine device effectiveness, including speech recognition and language development measures as well as patient-reported outcomes, have a strong emphasis on the patient's language background, including the mastery level of a language system. It is thus important to note that such factors may affect the interpretation and applicability of the results from the OUS studies.

Registries can be another evidence source and can be described as an organized system for the collection, storage, retrieval, and analysis and dissemination of the information on the persons who use a particular medical device. A registry is only useful if all relevant information is collected with good quality. Data collection and reporting should be performed as accurately as possible, and there is a monitoring system for the data collection to ensure data integrity.

In the recent years, there have been several initiatives for national registries on a variety of device types, such as cardiac devices. For cochlear implant devices, a registry is still in its early development. Recently, Sanderson et al. 2014 proposes a global patient outcome registry to collect data on prospective, multicenter, multinational patient outcomes with a focus on long-term outcomes, educational placement, and quality of life in pediatric cochlear implant recipients. Dr. Marinac-Dabic will go over the concept of utilizing registry data to support a premarket to postmarket shift in data requirements in pediatric patients in a minute.

To summarize, certain sources of evidence may not be appropriate or used exclusively to support premarket approvals for cochlear implants. However, for device modifications or other changes, they may become useful as supplementary evidence to

support a premarket to postmarket shift in data requirements. The Panel will be asked to discuss this concept as well as leveraging clinical data from adult and/or pediatric subpopulations, particularly older children.

In addition to data obtained from IDE pivotal studies, the following types of data have been used as supporting evidence for premarket approvals of device modifications for cochlear implants in PMA supplements. The Panel will be asked to discuss the scientific and clinical relevance of the following types of data that have been used as supporting evidence for premarket approvals of cochlear implant modifications in PMA supplements:

a. Unpublished adult and/or pediatric clinical data collected from prospective OUS studies;
b. Published findings from retrospective studies on data collected from pediatric patients; and
c. Prospective or retrospective clinical performance data obtained from a subpopulation of pediatric cochlear implant recipients (e.g., children at a relatively older age, such as 6 and older or 12 and older).

Also, the Panel will be asked to indicate if any additional source of evidence may be used to support the premarket to postmarket shift in data requirements for pediatric patients, particularly those who are younger than 6 years of age, for a specific device change, such as U.S. cochlear implant registry data, if developed in the future.

The overall benefit-risk profile is determined at the time of premarket approval. During the review of a premarket application, FDA may impose postmarket requirements such as continuing periodic reporting on device safety, effectiveness, and reliability for its

intended use, as well as conducting post-approval studies.

Post-approval studies are usually intended to help monitor device safety, effectiveness, and reliability for the intended use at the time of device approval under an original PMA application or a PMA supplement, especially if there is uncertainty about aspects including long-term performance, real-world device performance, effectiveness of training programs, subgroup performance, and outcomes of concern.

In premarket submissions of device modifications to cochlear implants, post-approval studies have not been often used as conditions for approvals, with an exception of a PMA supplement under SP12 speech processor, which was mentioned earlier, for the Nucleus 24 Cochlear Implant System. The approved device modifications included several changes to the programming and neural response telemetry software, in addition to a new speech processor and a new receiver-stimulator component.

As I mentioned earlier, the approval was for both adult and pediatric patients based on adult data from an IDE pivotal study. No pediatric data were made available as conditions for approval. Two postmarket studies -- I'm sorry. Two post-approval studies were required to provide confirmatory safety and effectiveness data, particularly for the pediatric population.

One study was on adult subjects and the other was on pediatric subjects, with a proposed sample size of 50 subjects in each study. The study design was comparable to that in the IDE adult study used to support PMA. Safety and effectiveness endpoints were determined at the 12-month interval post-activation. Studies on both adult and pediatric subjects were completed, and labeling recommendations were implemented after study

completion. This postmarket experience has shed light on this shift of data requirement from premarket to postmarket for premarket approvals of certain device modifications and other changes.

The Panel will be asked to provide comments on questions related to the clinical considerations in designing post-approval studies used to support this proposed shift in the pediatric patients.

Given all the information that we have presented, the panelists will be asked to provide input on some issues related to post-approval studies. That is, in the future, if FDA were to determine that it is appropriate for clinical data from older children and/or adult patients to support premarket approvals for pediatric patients, particularly those who are younger than 6 years of age, post-approval studies may be required in some cases to confirm safety and effectiveness in this population, as well as to inform future labeling.

The Panel will be asked to comment on the following:

a. The Panel will be asked to comment on the age-appropriate test metrics for children implanted at different ages (broken down into different age groups, e.g., 12-24 months, 3-6 years, 6-12 years, age 12 and older, and so on) to determine device effectiveness. The Panel will also be asked to comment on various outcome domains (e.g., speech intelligibility in quiet/in noise, spoken language development, quality of life, and so on) that should be examined in post-approval studies.

b. Children implanted at a relatively young age may require a longer-term follow-up period than those implanted at a relatively older age. The Panel

will be asked to comment on the appropriate follow-up period for the pediatric cochlear implant recipients (e.g., those younger than 6 years of age) in a post-approval study.

c. To confirm safety and effectiveness in a PAS, patient factors (e.g., developmental and cognitive factors, and pre- versus postlingual onset of severe to profound deafness) should be included in the study design considerations. The Panel will be asked to recommend any additional patient (or device-related) factors specific to the younger pediatric population that should be considered in designing a post-approval study to support a premarket to postmarket shift in data requirements.

Thank you for your attention to this presentation. In the next presentation, Dr. Danica Marinac-Dabic is going to present on the topic: Strengthening Our National System for Medical Device Surveillance.

DR. MARINAC-DABIC: Good morning, Dr. Woodson, Dr. Eydelman, distinguished members of the Panel, and the audience. My name is Danica Marinac-Dabic. I am the Director of the Division of Epidemiology in the Center for Devices and Radiological Health, and my division is in charge of oversight of all mandated postmarket studies that we ask our colleagues from industry to conduct for various reasons in the review process.

So we currently have over 300 mandated studies that we follow for various classes of devices. In addition to that, I also oversee a large portfolio of original research studies, and we currently have over 50 ongoing studies that are done in cooperation with our colleagues from academia. And, finally, one other major program that is housed in my division is a

systematic literature review program. And for your information, during the past 3 years we've actually conducted 124 systematic literature reviews to support our premarket colleagues.

So, with that in mind, my goal today is really to give you an outline and a very general update on what is available to actuate our decisions and also for you to recommend certain tools that we can utilize in a postmarket setting, since during the past several years there have been really major shifts in the paradigm of how we think about postmarket infrastructure and methodologies.

So, first, I was going to briefly talk about our vision for the national medical device surveillance system and talk about some of the recent implementation steps that we have undertaken. And you will see, there are going to be a lot of opportunities for the ENT field to benefit from some of these methodological infrastructure developments. Then I will give you an update on the public-private partnership called MDEpiNET that we have stood up, and now it's really a formal public-private partnership ready to accept the funding and ready to accept ideas to advance the medical device research.

And we'll give you a sense of how CDRH has been using registries. Obviously, there are not going to be many examples from the ENT world, but you will see what are the types of questions we nest in the registries that potentially can actually guide your discussion today. And then I will talk about some opportunities, maybe mentioning one example of the ENT registry and potentially see how that can be helpful in your deliberations today.

So, basically, I'd like to call your attention to this landmark white paper that CDRH had issued in 2012, called "Strengthening Our National System for Medical Device

Postmarket Surveillance." And also shortly after that, in 2013, we've updated this report again with specific steps that we're going to be taking in moving this forward. So these are two important documents that actually set the stage for many of the implementation steps that you will see from my presentation on where we are moving actually in a postmarket surveillance setting.

So the vision that we articulated in that paper really is that we envisioned a system that will communicate timely, accurate, systematic, and prioritized assessments of device benefits and risks throughout their marketed life cycle using high-quality, standardized, structured electronic health information. And we wanted really to have a system that will identify potential safety signals in near real time. And clearly we are far from that vision today. There are lots of tools that we're using, but they're all compartmentalized in various parts of our Center. And, really, there is not much integration with the data sources that are available in the areas that you are actually playing a major role in.

So we felt, if we had such a system, we would be able to reduce the burden on postmarket surveillance and we will also be able to facilitate the clearance and approval of new devices. And this is really why you're here today.

So what we felt at the time when we issued this white paper is there are four major actions that we were committed to do. The first one is really to establish the Unique Device Identification System that will be really the means to identify specific devices in the data that are captured in the Electronic Health Information. Then we also decided we were going to promote the development of the national and international device registries for selected products, modernize adverse event reporting and analysis, and develop and use

new methods for evidence generation, synthesis, and appraisal. So as you can see, this was a very ambitious agenda, and many of these things are already moving in phases, and I hope, throughout the day, we're going to have a chance to actually tackle some of these.

So we have not just issued those white papers. We actually have taken some specific steps to implement them. Two major and important things that I thought you should know about is that we have convened the planning board, which is the national multi-stakeholder planning board. It has 20-plus members from all various sectors from healthcare, and it was run by Brookings Institute. And also, this planning board just completed one full year of deliberation and published the report, which actually talked about the first steps on how we are going to start a national system.

Then we also convened a national registry task force, which is done via our public-private partnership and Duke Coordinating Center, and also talked about how the registries can actually help the FDA and the rest of them -- the healthcare ecosystem.

So, basically, the bottom line is that the system that we envision is going to have in the foundation the registries of medical devices or registries that contain medical device information linked with UDI where it's implemented in the Electronic Health Information. So, basically, you can see that we are initialing the system, that it's very much embedded in our national learning healthcare system. All of the data tools, such as mandated postmarket studies, such as MedSun hospitals, adverse event reporting, Sentinel data, adverse -- I mean the claims data, all of these are very important, but they are going to be supplementary information.

So this is the Brookings report that I cited here for your reference, and I encourage

you, when you have a chance, to take a look. It really speaks to our national system, not FDA's system. We really know that we cannot do this alone. So it has to be a value to all of you and to us in order for this to succeed.

The Medical Device Registry Task Force report is not out yet, but we are planning to launch for the 15th of June. So stay tuned for this one. This is going to also shed some really innovative ways of thinking about registries in the context of regulatory science.

So now I'd like maybe to use the next couple minutes to talk about the public-private partnership called MDEpiNET, which, in fact, it had been set up even before that vision had been articulated in 2012, with a vision to develop the national and international infrastructure and innovative methodologies for robust studies and surveillance that will be able to enhance our ability to study performance of medical devices throughout the entire life cycle. So this was the first public-private partnership that was set up with that goal, focusing specifically on devices.

So since that time we have made great progress, and we've established the methodology and science -- methodology center for MDEpiNET at Harvard University, also infrastructure center for MDEpiNET at Cornell Weill Medical College, and we started immediately piloting projects to showcase what can be done when we actually join forces with external stakeholders.

So we issued a series of grants. A total of close to $12 million has been actually invested in development of this public-private partnership with over 50 studies under way. We certainly hope that we will, in the near future, have the studies that will be actually discussing all these important questions that the ENT field may actually have for this

consortium. Then last year we moved that from purely FDA funded and to public-private partnership and integrated also that in our internal CORE system. So, for example, our post-approval studies program, our 522 program, evidence synthesis program is really taking on methodologies that are being developed through the public-private partnership, and we're applying those as we speak.

And just to give you a sense, we have an MDEpiNET stakeholder council, which is a broader entity that oversees it, and we have these three coordinating centers in leading universities. And we also have a number of committees that actually are moving forward, you know, stakeholder engagement, research and publication committee, executive operations committee -- and I'm sure you're familiar with the typical structure of the public-private partnership.

We currently have two ongoing working groups in orthopedics and cardiovascular, and we hope to actually expand that to all panel type of devices that actually -- how the FDA panels are structured across all of these devices, in the next several years.

And to give you a sense of who actually is in the MDEpiNET, I wanted to just share this quick -- of these logos. So you will see, there are our colleagues from industry. AdvaMed is actually very much represented. Other organizations as well, specific individual members from industry, professional societies, registries, academia, payer-patient organizations are playing an active role in this public-private partnership.

Now, going back to why we are here and how the registries can actually be utilized for regulatory science in MDEpiNET, so there are several buckets that I'd like to just share with you and give you a snapshot of how we've been using registries at CDRH. We currently

use registries for post-approval studies, meaning if we approve the product and there's conditional approval attached to it, there is a likelihood, if there is a national registry that's out there, that we're going to be encouraging the companies to leverage that registry. So, for example, we have -- in the areas of cardiovascular and orthopedics, we leverage a number of national registries and also international registries to nest the post-approval studies in them. So that's one big bucket.

The other one is that we facilitate new registry development. So we are spending actually some seed funding to motivate when there's a need to push a little bit the clinical community to think about a registry. So we do that. And we also help very much in designing the data collection tools and work with the companies to bring them together. So you can see, in the areas of external defibrillators, for example, transcatheter aortic valve registry, IMPACT Registry, PROFILE, which is in the Society of Plastic Surgeons, and others, we've actually done that role of facilitation and scientific partner.

We also use existing registries for discretionary studies. For example, if FDA has a question that it's not really a question that we can pose to any member of industry, who actually do their own funded studies, we actually do that on our own dime. And we have a number of these discretionary studies that have been completed and informed us both premarket and postmarket.

So we also explore registry capabilities for active surveillance. For example, we funded the development of the software called DELTA, which is now embedded in NCDR's suite of registries in cardiovascular, and it's actually in the background picking up the signals on potential poorly performing devices using propensity score matching, and it's really

having a really neat tool to add to all of the really great quality of tools that those registries have.

We also build methodological infrastructure for registries, and I just listed here three international consortia that we developed during the past 3 years, one in orthopedic field, one in cardiac field, and one in vascular field.

And we also use the registries to expand indications, meaning that if there is a national registry and if the product had been used already and if the data aren't collected that can support expanding indications, we no longer ask companies to do their own funded IDE trial. We actually can leverage that postmarket data, and that data can be used for expanding indications.

So I'd like to give you now three examples of successes to give you some ideas of what's working.

When Transcatheter Valve Therapy Registry was set up, this was in response to our approval of the first transcatheter aortic valve replacement, which was really a huge game changer and gave a great opportunity for seniors, who couldn't actually have open heart surgery, to undergo the surgery and get the valve replaced that way. So we worked with professional societies. The registry was stood up almost a month after the approval of the device. And what we've done, we've nested the post-approval studies in this registry. So this decreased the post-approval study burden and increased the overall capture that FDA has direct access to and allows for studies for expanded indications. Shortly after that, we actually expanded the indication to utilizing these registries solely based on the postmarket data. And we also will be using these registries for -- will be a basis for surveillance. So, as

you can see, if there is that kind of registry in the ENT space, these are the kind of things that we could do if we are able to set it up.

So another great success has been in the international space, called ICOR, International Consortium of Orthopedic Registries. So what we've done, we invited to the FDA all 29 existing registries in the world in orthopedics, and they all came actually to the first public meeting that we had, including one registry for Malawi, that they were just setting up one small registry. So even they came, which was really a great success. All eight of these registries are currently contributing the data, four million patients, and we can actually run comparative effectiveness studies and comparative safety studies in these. So we've actually done that and published 27 papers on this, and they're published in *JBJS*, which is the leading orthopedics journal.

We also developed the methods for combining these de-identified data without data actually leaving the registries. They could stay behind the firewalls, and we provide the actual codes. Registries run them there, send the summary statistics, and there you go, you have the best way of estimating how this combined evidence looks like. Again, it had been contributing to our knowledge of orthopedic devices.

And, finally, one area which I think would be dear to our premarket colleagues as well -- and we're working very closely with cardiovascular division with that -- is the program that had been established under this MDEpiNET public-private partnership called PASSION, which stands for Predictable and SuStainable Implementation of National Cardiovascular Registries. And we launched it last year, within a year. If one can nest clinical trials, IDE clinical trials, in existing registries, one can really save lots and lots of

funding. And we have great examples from Sweden, where really the clinical trial costs very, very little in comparison with what it would cost here, because the national registry had been utilized. And not only in Sweden, but we had an example from here. When SAFE-PCI for Women was run through NCDR's suite of registries, the cost was cut 65% because the national registry infrastructure was used.

And so, basically, these are the kind of things that I wanted you, the Panel, to know how the FDA is thinking these days and that we're beyond this traditional one-off post-approval studies, and then we can be more integrated in what healthcare delivery is all about.

So now I have only one slide that focuses really on cochlear registry efforts, and it's just to shed some light on this registry. Maybe you already know about this, but this is the Cochlear Paediatric Implanted Recipient Observational Study, and essentially it is an international registry. I believe it collects data from India, Indonesia, Australia, China, Turkey, and Vietnam. And there's a huge plan to actually expand to other countries. But it is a prospective, international, OUS patient outcomes registry for children that are younger than 10 years of age, and it collects also demographic data, comorbidities, device use, auditory performance, quality of life, which is also very important, and health-related utilities. There is pre-initial activation or baseline characteristics and also every 6 months during 2 years and annually thereafter. So there is a citation from *BMC Ear, Nose and Throat Disorders*. But then again, that's another example of how the sponsor-initiated cochlear registry can actually change the landscape of how data can be collected.

So how that fits with everything that you heard today about pre-/post-shift, and you

know, there is our Strategic Priority No. 2 that talks about striking that wide balance between pre and post. And really what's important, you saw probably our guidance documents and this one particularly, finalized just earlier this month, where we, in fact, are thinking about where that middle can be moved and how much of the data can be shifted to postmarket.

So, basically, the entire development of this national system that I talked about was done with an idea that we would need to have a functioning postmarket integrated national system in order for our colleagues from premarket to be able actually to shift data collection in the postmarket setting. So that's why we are working very hard to be of service to our colleagues in the premarket setting to actually lay out not just infrastructure but also methodologies.

So I think I would conclude here. And if there are any granular questions about these data sources, I also have my branch chief, Dr. Christopher Ronk, here with me, who is actually overseeing these devices in my division. Maybe he'll actually speak more later if you have questions about our post-approval studies that have been completed and also this one. And if you want to contact us, there are multiple e-mails, whether it be FDA or in the MDEpiNET public-private partnership.

Thank you so much for your attention.

DR. WOODSON: Well, thank you very much.

Does anyone on the Panel have any clarifying questions for any of the presenters?

Yeah, Dr. Chandrasekhar.

DR. CHANDRASEKHAR: Sujana Chandrasekhar.

I'm concerned that prelingual deafness is defined as younger than age 6 by FDA, and in practice, we consider prelingual deafness to occur before age 2 or 3, and I think that definitely will cloud the deliberations subsequently.

DR. EYDELMAN: I'm going to ask Dr. Shu-Chen to address --

DR. PENG: I appreciate the comment. And as you mentioned, I mean, there's no definite way to define pre- versus postlingual because the early childhood language developed in a continuum manner. So we will not object to any proposed cutoff, as long as it's appropriate and fits the direction of where we are going. Yeah.

DR. NANDKUMAR: So I think the age 6 years was just used as an example to kind of differentiate between the subpopulations, and most cochlear implants today are approved for 1 year and above. And we are open to the Panel's recommendations for where that cutoff would be.

DR. WOODSON: Any other questions from the Panel?

DR. NORTON: Hi, this is Susan Norton.

I am confused by the number of things you include in the proposal to go from premarket to postmarket approval. And a waterproof covering is very different than a change in processing strategy or device design or a speech processor. Can you clarify more whether you want information on specific aspects? And can we separate waterproofing from speech processing strategies?

DR. NANDKUMAR: So the idea behind the presentation was to kind of lay out the entire scenario of the different kinds of changes that could exist in cochlear implant technologies that are upcoming or that we have seen until now and so on. We are

completely open to the Panel recommending some kind of a tiered approach, if you would like, something where certain changes maybe are more suitable to extrapolation and certain other changes may be more suitable to a registry kind of study or something like that.

Now, this is where a more focused post-approval study may be more appropriate. So we are not looking for, like, specific changes that you are putting out, but maybe more of a philosophy, like what would be appropriate. What kind of patient factors should be considered in those approaches for the pediatric patients?

DR. NORTON: So I have another question. So in the case of cochlear implants, there are multiple providers involved in the ultimate success or failure of a child with a cochlear implant. Surgery is just the first step, so in terms of qualifications of the surgeon's surgical techniques, safety of the internal device. And then there's all of the programming that goes on by the audiologist, unlike the devices you cited for the registry, where most of those are -- they're dependent upon the skills of the surgeon and there are objective measures in terms of, you know, is your heart pumping better compared to a cochlear implant? How would you propose to account for all of the sources of variability in each of the stages associated with the success or non-success of a cochlear implant?

DR. EYDELMAN: So you're absolutely right, this is a complicated question, hence the Panel meeting today and our request for your thoughtful deliberations.

DR. MADELL: Jane Madell.

In the list of changes in indication for use, I would like to suggest that we consider age at implantation. The current indications are not -- the current FDA indications are not

what's happening clinically. People in large centers are universally implanting younger children and infants, and people outside the U.S. are routinely implanting children younger than 12 months. And from the data that we have indicating the significance of age of implantation and length of use, I think it's something that needs to be added to the consideration for changes in indication.

DR. NANDKUMAR: We appreciate that. I think that's one of the question which says -- that asks for additional recommendations for those kinds of changes.

DR. KENNA: I just have a process question. This is Marly Kenna. In terms of registries, what type of registries exist within the United States? It sounds as if there's a registry that's been developed outside the U.S.

DR. NANDKUMAR: For cochlear implants, you mean?

DR. KENNA: Yes.

DR. NANDKUMAR: I think that was the one that we found that was published.

DR. KENNA: Um-hum.

DR. NANDKUMAR: And that's why we cited that.

DR. PENG: This is Shu-Chen Peng.

That one is not even originated from the U.S. So basically there is none.

DR. KENNA: There is none.

DR. PENG: Right.

DR. NANDKUMAR: We are aware, however, of the American Cochlear Implant Alliance, which has recently formed and is apparently actively setting up a U.S. cochlear implant registry. Perhaps some other folks in the audience here may be better equipped to

give you more information of where that effort is.

DR. KENNA: It certainly sounds as if that's something that we would need as part of our recommendations and perhaps something we could partner with the FDA's expertise in developing it because we're developing a registry just for a rare disease and it turns out to be a lot harder than it looks. So help is definitely needed.

Thank you.

DR. HIRSCH: Barry Hirsch.

Just taking up on what Dr. Norton said, is it implied that the waterproofing on the devices is restricted for use by children currently?

DR. PENG: No, that does not imply.

DR. HIRSCH: So why are we going to be asking for children to be able to use a waterproofing device?

DR. PENG: So the question actually came from -- Dr. Won actually mentioned -- you know, when he was giving the waterproofing as an example, he mentioned about the usability issue, like it really depends on the design of a feature, like how much knowledge the kid needs to have in order to appropriately manipulate the device in the intended way. You know, that would affect -- so it's more complicated than just a device feature, if you turn it on or off. If you design something that requires some in-depth knowledge to be able to program and use it correctly, then it may challenge the kid to -- especially those who are younger in age who cannot report, it will challenge them to use it correctly. And it may introduce effects in effectiveness or even have the device broken, you know, in some fashion. So that's the kind of thinking. But, again, this is just given as an example. It's

really not that we are asking any clinical data to have this feature approved. It doesn't mean that. Yeah.

DR. BRIETZKE: This is Scott Brietzke.

It was mentioned that there was one specific example as part of the premarket approval, that a postmarket study was part of that process, and it was mentioned that that study was completed and the labeling recommendations were implemented. This is Slide 44. I'm just curious. What was learned from that experience? As we're considering expanding it today, I'm wondering what lessons were learned.

DR. PENG: So just to give you a little more information than what we mentioned. So what happened at that time -- it was, like, back in 2007 and 2008 -- there was this new speech processor called SP12 that got introduced, and at that time the only clinical data that were used to support approval was from adults, and there were some questions about the pediatric -- the effectiveness used in the pediatric population. But the concern at that time was not big enough, like there wasn't any safety concern to trigger the consent to limit the indication in pediatric population. And at that time, that was around the time when FDA had the initiative of using the post-approval studies to -- it's kind of a similar thinking as this, but it was a little less, you know, involved.

But in the pediatric study -- so we mentioned -- so there were two studies, one in adult and one in pediatric. In the pediatric study, the study subjects were all -- who were qualified were those who were age 18 and below, and the test metrics used were the same like you see that were age appropriate. And specifically FDA asked the sponsor to include IT-MAIS and MAIS that are suitable for very young infant -- you know, children aged one and

above. And the study was completed. The study, actually it was -- the study period was 12 months. It wasn't as long as we are thinking now. You know, we have a question about the follow-up period. But, again, that was just to serve as the confirmatory information to confirm the thinking at that time.

DR. ISHIYAMA: Ishiyama from UCLA.

I have a question about this -- this was not covered today at the presentation. But in the material that was handed out before the meeting, you have a section on a summary for medical device reporting events, MDR, and there are a lot of things written there, including death. Is this data from all comers? Is there any particular breakdown from a pediatric population, in an adult population? And also there was nothing, I think, mentioned here regarding the reliability of the speech processors, because in a clinical setting they are known to fail very frequently.

DR. NANDKUMAR: So the data that you see there is based on the MAUDE database, the adverse event reporting database that we get. Like, I think we spoke to that a little bit yesterday, which is that there is a voluntary component and a mandatory component on the reporting. Now, I don't think there are certain thresholds for reporting. I don't know how many reports there are for speech processors and reliability kind of issues. We are working with the AAMI standards group to come up with a U.S. cochlear implant standard which will address better the reliability reporting of cochlear implants, which will then include reporting on the implants and the external portions. Right now, the data that we have from the MAUDE does not differentiate between externals and internals and long-term reliability.

DR. ISHIYAMA: What about the breakdown from a pediatric population and adult?

DR. PENG: What do you mean? Do you mean the differentiation between -- you mean --

(Off microphone comment.)

DR. PENG: It's in the appendix, Appendix 2 or -- Appendix 2. Could you clarify your question? You said pediatric versus adult. Is that what you were asking? It's really just how we have the data retrieved. You know, we put in a parameter for age and take the data that way. And also you mentioned that it is just to clarify that from. I think there's a note in the appendix, or somewhere, that says that we are not saying that the death has to do with the implantation -- the implant itself, because all the medical events got reported. So it's not clear. Yeah.

DR. NANDKUMAR: And I would also advise that that data should be -- you know, please keep in mind that, for that data, we get sometimes incomplete reports, the age at which the adverse event sometimes is not reported, so that analysis is based on what was reported.

DR. WOODSON: Go ahead.

DR. KENNA: Along those similar lines -- and I'm looking at the data that's in that supplement. It wasn't clear to me what the time frame is for required reporting of complications. It looks like it was 6 to 12 months, but I think -- and perhaps I'm incorrect, but I think those of us who do implants find that very often there are things that happen much later than 12 months. So perhaps, as we discuss this, there should be some change in the mandatory reporting of complications or malfunctions or something like that.

DR. NANDKUMAR: So we do get follow-up reports. There is no, like, limitation on the time frame like that. So the manufacturer reports and then we have follow-up reports afterwards, either from the manufacturer or it can be from the clinics. So there is no limitation as to the -- that it should end at 12 months or something like that.

DR. EYDELMAN: In other words, as a long as a device is implanted, the same regulation applies, the need to report any adverse event.

DR. WOODSON: This is Dr. Woodson.

So, to clarify, the data that you've shown there are just some numbers that you've extracted, and there is more detail in the study. So if you wanted, could you go in and find out when and why the patients died? Because right now, it's kind of like when we look at patients that have been treated for cancer, we divide it into disease-related deaths and non-disease related deaths. Is that type of information available in this database?

DR. NANDKUMAR: Yes. And, again, it depends upon -- if it's not, we have the ability to go follow up on those. Sometimes it's available, and sometimes it depends on the facility that's reporting and the follow-up.

DR. EYDELMAN: In other words, we can. If the Panel recommends to dive deeper, we can do that. However, what Nandu is trying to point out is sometimes our efforts are limited by what's actually reported.

DR. WOODSON: And I guess this is a good example of how a registry would allow you to prospectively collect the kind of information that really helps us to make decisions.

DR. EYDELMAN: As well as educating our colleagues in academia and practice on the need and the importance of this data.

DR. MARINAC-DABIC: Malvina, I want to just add one more thing. Although I'm not the individual that is in charge of MDR reports, but as you know, there are clear limitations associated. We've heard that in terms of the MDRs. And, you know, one thing from the epidemiologic perspective which really kind of gives us the word of asking for more registries, it's just the specific questions of the lack of a denominator. And the numerator is already questionable. So if you really want to make an informed decision, you really have to understand not just the content of what is driving the safety, you would like to also think about the benefit side of it because it's always that balance, which you don't get if you only look into reports.

And the other thing is that rates cannot be calculated based on the number of reports, even the number of events. After duplicates had been cleared or excluded, that doesn't really represent the rate of that. So we use them very, very much in our processes, but they have their limitations.

DR. WOODSON: Yes.

DR. NORTON: Susan Norton.

So as someone who works exclusively with pediatrics, I find going into MAUDE extremely frustrating because there is enormous variability across the companies, in the information they provide about the type of device failure. There are many internal device failures related -- well, related to manufacturing problems, for which they acknowledge there's a manufacturing problem, but there are not true diagnostic tests, integrity tests, of the device before you take it out. And will the FDA -- and there is no -- I understand from talking to people in industry that censors do not routinely return explanted devices to the

manufacturer for analysis. So there are multiple levels with tracking defective internal devices and identifying the cause of the device failure and how you define it, which are particularly critical in pediatrics where, in young children, the patient cannot report adverse effects. So, as part of this process, are you proposing to strengthen the reporting requirements for manufacturers, in terms of failed devices?

DR. DASIKA: Yes. So those are excellent points, Dr. Norton. I think one effort that FDA has been a part of for the last 4 to 5 years is to help improve the quality of reporting. As you say, there are clearly differences in the manufacturer's ability and the consistency of reporting across devices right now. But FDA has been involved with the AAMI standard that Dr. Nandkumar mentioned, the Association for Advancement of Medical Instrumentation standard. FDA is one of the stakeholders at the table, along with three cochlear implant manufacturers approved in the United States, as well as the European company as well. So four cochlear implant companies in the world, FDA, and several leading academicians and clinicians are at the table too.

So as part of that standard effort, we are basically writing into that standard best practices for reporting, so what will be reported to MAUDE, and that will include every explanted internal device right now. And, in addition, there will be more clear requirements for reporting on the external components as well, so that hopefully will help to improve the lack of consistency that there is right now.

DR. EYDELMAN: So just back to what was said already. There are two inherent issues. One is lack of clear guidance about what needs to be -- what should be reported for this particular device, and second, lack of awareness by the clinicians as to what and how to

report. So I just want to give you an example from a different device area. For example, in IOLs -- we're also in charge of ophthalmic devices in my division.

So, for example, during the outbreaks related to contact lenses, we have partnered with the professional ophthalmic organizations. And after we developed a template of what should be reported for problems with contact lenses, we actually posted the links at the website for the ophthalmic professional organizations because that's a site the clinicians are more likely to visit than the FDA's site. And we actually have seen a significant improvement.

So, hopefully, after we come up with the recommendations -- and obviously, we welcome any input that the Panel would like to make today as to the key parameters that you believe need to be included in the reporting of problems, adverse events, with pediatric cochlear implants. But, in addition, hopefully once we're done we will be able to partner with all of you to try to disseminate the recommendations and actually make them have an impact.

DR. WOODSON: Thanks.

Dr. Madell.

DR. MADELL: Jane Madell.

In the reporting of failed internal devices -- and internal and external devices are such a different area, and we really need to think about them separately, as everybody knows. But the internal device problem, you know, there's the category of soft failures where the clinician is sure something is wrong -- the audiologist, speech language pathologist, auditory verbal therapist are sure something is wrong and the device is

removed, and when it goes back to the manufacturer they can't find something wrong with it, but the child's been reimplanted and is doing much better. So, clinically, it is clear that something was wrong. Even though the manufacturer can't identify it, they don't report that as a failed device because they haven't found something wrong, frequently. But that needs to be added to the things that get considered in the device failure list.

DR. EYDELMAN: So, just to clarify, we collect adverse events with a device, not with a procedure.

DR. MADELL: I know. But if the clinician -- if the manufacturer -- when the manufacturer evaluates the device, if they can't find something wrong with it, they don't report it as a failed device.

DR. NANDKUMAR: So the standard that we are developing is going to address just that case. It's under a category called "no fault found," and they are actually going to report that as a failure.

DR. DASIKA: Right. So, yeah, it will have to be reported because it's an explant. But then if the manufacturer found it to be functioning at the time of their testing, it would go under that bucket or that category of "no fault failure."

DR. MADELL: Well, if they can't find the failure, that doesn't mean there really wasn't something wrong.

DR. NANDKUMAR: Right.

DR. DASIKA: Right.

DR. MADELL: It means they haven't identified it.

DR. DASIKA: Exactly.

DR. NANDKUMAR: So even if the device is in spec when they're tested, it will still be reported as a failure because of an explant.

DR. DASIKA: Yeah. And maybe just to add. We are considering a very broad definition, sort of, of failure, which is failure to provide clinical benefit for the patient. So any device in that sense that was explanted from the patient failed to provide the clinical benefit for the patient, so it would be reported as a failure.

Thank you.

DR. KENNA: Marly Kenna.

So I think this is a great discussion, and I think the series of questions before the Panel today, to me at least, break down into two groups. One are devices that already exist or may actually already be in place, where we're considering software or existing things, like waterproofing, that are either in place or for which we don't have perhaps as much concern or we have more data from the adult world.

And then there's the other side where I think a lot of these safety questions come. If we're expanding indications, for example, single-sided deafness in a 3-year-old, I think there we're going to be looking very hard at the safety questions of the devices themselves plus the efficacy data, which may or may not exist in adults. So, at least for me, these sort of break down into two big groups, and I think one set of questions may be more straightforward to answer than the other.

Thank you.

DR. ISHIYAMA: Ishiyama from UCLA.

Again, in the material that was distributed for the meeting, and also in the appendix,

there are three companies that have quite different requirements to designate a child to be a candidate for a cochlear implant -- an implant candidate, depending upon the audiologic profile, duration of hearing aid use. I think by allowing a liberal definition depending upon who is the manufacturer, it's causing a little bit of confusion in the clinical setting. Would you please clarify why you're allowing such a liberal definition based upon the manufacturer?

DR. EYDELMAN: So usually we determine the patient population at the time of the PMA approval. In other words, we'll look at the device characteristics and look at the patients studied in the clinical trial and make a determination based on the data, data about the device and data about the actual clinical trial, about the appropriate patient population for that particular device. In other words, we're not making a decision about the types of devices. We're making a recommendation for a patient population specific to that particular device. Hence the inherent differences between the devices.

DR. NANDKUMAR: The indications for use that you're looking at in the appendix that was given for each manufacturer, those were what the manufacturer proposed at the time of the PMA that was approved between 1997 and 2001, during that time when the initial original PMAs were approved. And so those indications are from then, based on each manufacturer and what they presented, their device and their data. So we don't have a way, at this time, to kind of make it all uniform. It's the manufacturers to come in, and if they feel like they can expand --

DR. EYDELMAN: Well, it's whether they feel that they can expand and whether we believe that it's appropriate or not. In many other device types, it is quite frequent to have

different indications, and very often it's how we limit the patient indication, the IFUs, indication for use, based on the data we see. In other words, the sponsor can propose (a) or a particular bucket. And then after we review the data and we don't believe it's appropriate, then we recommend a smaller indication for use. That's quite common in all other device types.

DR. ISHIYAMA: I think, in a clinical setting when a child has profound deafness and everything is equal, I think it's rather confusing when Manufacturer A says you have to use a hearing aid for 6 months and others will say 3 months is okay.

DR. EYDELMAN: Having said what I said, I mean, we're very open to listen to your recommendations, and if you believe that there is something that we need to go back and take a look at, we're happy to do that.

DR. TOMBLIN: Bruce Tomblin.

Just maybe to clarify then. Are the use guidelines and so forth -- is motivation for changing or action to change on those, can it come from the FDA rather than from the manufacturers? Let's say, for instance, lowering the age of implantation guidelines. Is that something that requires the manufacturers to come to the FDA and propose, or is it something the FDA can initiate on their own?

DR. EYDELMAN: So the sponsor has to come in with their application for us to act upon it. However, we sometimes issue general guidelines, which then makes it clear that we're open to the suggestions.

DR. WOODSON: Dr. Kenna.

DR. KENNA: Along those lines, I think, although the manufacturers do have in

writing different guidelines for the use of their device or when you would think about using that . And I think, in clinical practice -- I can only speak to our own center. I think we view the need for how long you use a hearing aid or whether you use a hearing aid before a child gets an implant, I think we view them quite similar for all three devices.

So in thinking about this, if you just said you can't change the rules, but if you saw that in clinical practice, especially in some systematic fashion, that this was being used differently clinically, would the FDA be able to develop or have some conversations with the manufacturers about what's really happening in the real world? Sort of like the soft failures versus what's actually in writing, because I know what we do is quite different than what is written down.

DR. HIRSCH: Another way of phrasing that is, I think that implants are done maybe about 50% of the time in an off-label use based on -- it's just an estimate, but I think it's at least 50% based on the requirements for their hearing age of implantation, as you mentioned, to go down to 9 months. There are lot of factors that are bringing them to this off-label use.

DR. WOODSON: Dr. Houston.

DR. HOUSTON: Derek Houston.

Yeah, I just wanted to clarify following on Bruce's question -- Dr. Tomblin's question. And correct me if I'm wrong. I don't think that the PMA has to come from the sponsor. It could come from me, right? I could propose for age of implantation to go down and submit an IDE to do a study.

(Off microphone comment.)

DR. HOUSTON: The IDE can come from them.

DR. NANDKUMAR: The IDE can come from sponsors and investigators.

DR. HOUSTON: Okay.

DR. NANDKUMAR: The PMA is always the manufacturers.

DR. HOUSTON: Okay. So I can submit an IDE to do a study to look at age at implantation, and then that could, I guess, be used by the manufacturers to submit a PMA.

DR. EYDELMAN: If they choose to.

DR. HOUSTON: If they choose to, right.

DR. WOODSON: Do you have a question? Are there any other questions or comments from the Panel?

(No response.)

DR. WOODSON: I think this has been a very good discussion. I think we can take a 15-minute break now and come back at 10:25.

(Off the record at 10:09 a.m.)

(On the record at 10:35 a.m.)

DR. WOODSON: Okay, let's get started again. I think our Panel is all assembled. The FDA has invited three guest speakers, who are experts in this field, to provide the Panel with information on the medical devices that are being discussed today. We will hear all three presentations prior to a question and answer period from the Panel. I want to thank all of you in advance for being here today.

I would first like to call on our first speaker, Dr. Laurie Eisenberg. So please state your affiliations. You'll have 15 minutes.

DR. EISENBERG: Just one affiliation. I'm at the Keck School of Medicine at the University of Southern California. And in the interest of disclosure, I'm listing three conflicts of interest.

So I've been asked to speak today -- speak on speech recognition hierarchy, which is sort of an issue that most clinical audiologists intuitively think about and use in their daily practice, but we've formalized it for research, for some of our research protocols.

So why would we want to use a speech recognition hierarchy for children? Well, first of all, the ability to recognize speech improves as the child matures. So young children may not have a complete set of phonemic categories, such as they may not appreciate the salience of some of the important cues for speech.

Young children may be restricted in vocabulary. In fact, it's important to note that you would not give a sentence test to a 2-year-old child because they probably don't have the vocabulary and may not be speaking in five-, six-word sentences.

And then also articulation is developmental. And we're speaking about normal hearing children now. So even children with normal hearing will have deficits in their speech production, and in a word recognition test or a sentence recognition test, this is going to impact how an audiologist would score the test if the child, in fact, has speech production deficits.

So considerations in assessment based on developmental age. And, again, I'm sort of referring to children with normal hearing or typically developing children. We have to concern ourselves with different options. And you heard some of these this morning concerning do we administer a test of materials that are in a closed set where you have

choices or an open set?

Stimuli. The audiologists will have to choose if it's going to test just looking at phonemes or nonsense words or monosyllabic words, multisyllabic words, or sentences.

A decision has to be made about testing in quiet versus background competition. And in most cases we think about -- in most clinical trials they have spent time looking at in quiet, but testing in competition is important, and it does add challenges to the listening situation.

Modality. Again, we usually test auditory only when we do a clinical trial or part of a clinical trial. But, in fact, multimodal processing is quite important in the development of speech for children. And there are advantages to testing auditory only and visual only and auditory/visual. Many of the children may not have very good speech recognition and have to rely on visual cues.

Then again, live voice versus recorded presentation.

And, finally, age-appropriate responses. Is it a picture-pointing versus a verbal repetition? So, in most cases with very young children, we will do a picture-pointing closed-set test.

Okay. So why would we then need a hierarchical approach for children on top, over and above just the normal development? And that is hearing loss adversely affects speech recognition -- no surprise -- and that speech recognition abilities decrease with increasing severity of hearing loss. And so maturation will, in fact, interact with the degree of hearing loss, and a hierarchical approach will reduce -- can help reduce floor and ceiling effects. You're not spending time testing the child on materials that are too difficult or too simple,

especially when you have a very young child who has a limited attention span.

So what are some of the factors influencing speech recognition in children with hearing loss?

One, age at identification/intervention. So it's not just simply that a child has been identified with a profound hearing loss. When was that hearing loss identified? When is the child placed in intervention?

Duration of auditory deprivation. That was a major factor at the very beginning of cochlear implants. And I can tell you, having worked on the very first clinical trial of children with a single-channel device, the approximate age of receiving a cochlear implant was around 8 years of age.

Developmental age versus hearing age. So developmental age is -- you know, a child may have a certain chronologic age, but does that align with their developmental age? But we will particularly see this with children who might have cognitive delays, might have underlying autism. And the hearing age, so a child at 5 getting identified and fitted with a sensory device, the day that they're fitted, we have come to call this now the hearing age.

And fitting and effectiveness of a sensory device. Not all fittings are the same and effective.

The quality of an intervention program. And this can be quite controversial.

Communication modality. A child who is speaking -- is not speaking -- I'm sorry, who is communicating in American Sign Language probably won't be able to be tested as effectively on an open-set recognition test. And if they are, it may be very difficult to score their responses because of their speech production.

And, finally, what's becoming more and more known to all of us is the importance of the home environment and parental factors. The contributions of the parents cannot be understated. Okay. Or overstated.

So I'm going to be talking specifically about a speech recognition hierarchy that's been adapted for an NIH-funded study that's now going into its 30th year, and it's the Childhood Development after Cochlear Implantation, or I'll be referring to it as CDaCI. And the principal investigator is John Niparko.

This study began enrolling children with severe to profound hearing loss between 2002 and 2004, and you can see the number of children enrolled during those 2 years. And this is also a multicenter study, and you can see the different centers from around the United States that participate. This study also has a control group of children with normal hearing.

The study design is following children on different domains of development, language, psychosocial, quality of life, but I'm going to be focusing on speech recognition. And the design is baseline, pre-CI surgery where all the protocols -- there are assessments for all the protocols, then surgery, and then postsurgical follow-up.

So, for speech recognition, we developed a test battery really simply based on tests that were being used for most of the clinical trials at the time and most clinicians of major cochlear implant centers were using with their population. And you can see that it's sort of segmented by age of child and by skill set.

So we start with auditory behaviors, closed-set identification. And here's two tests, ESP, Early Speech Perception test, and Pediatric Speech Intelligibility. And then we move

into open-set tests, three different word tests, MLNT, LNT, the Lexical Neighborhood Tests, pediatric phonetically balanced word list for kindergarten age, and then the Hearing in Noise Test, which is a sentence test specific for children.

And to progress through this hierarchy, a child must be of a certain age, developmental age, chronological age, whatever the requirement of the test mandates, and a certain specific level must be achieved at each level to advance to the next, more difficult level.

Nae-Yuh Wang, who is the biostatistician on this study at Johns Hopkins, came up with the Speech Recognition Index in Quiet. It's called the SRI-Q. And he's simply taken these tests with an underlying assumption that they do progress in order of difficulty and ordered them on this scale.

I'm going to show you data now out to 5 years. We're in the process of analyzing the 8-year, and hopefully that will be coming out fairly soon. But you can see, at 5 years, we're looking at the distribution of this population as they progress through successively more difficult tasks over their follow-up intervals. And these data show the median data of the sample, the top 90th percentile, 75th, 25th, and 10th percentile. This characterizes what we all know about this population, that variability is quite, quite large. One way to look at these data -- what's being coded is, at each interval, the highest test a child reaches and what their score is, is coded on this index. So you have a lot of data points and then these regression lines that capture the different percentiles of the sample.

One way to look at it is at this middle point here, where we go from closed-set to open-set tests, and you can see that, if we want to see by these percentiles, at what point

does a child progress from closed set to open set, which really is sort of the gold standard of performance. You can see, for the top 10th percentile of the sample, by 1 year with a cochlear implant, they're now into the open-set word tests. The median of the sample takes about 2.5 years. And then we come to our lowest 10% of the sample. You can see, by 5 years, they're either around detection or a pattern perception, some getting into closed-set word identification.

Okay. And I'm going to be talking more about this sample. Okay, here's an example of a child that we followed who was from the United States, who went to Europe, the family went to Europe for an auditory brainstem implant because it was before a time that the FDA was receptive to a safety feasibility study on the ABI in this population. So these children go to Europe, and they come back and they need facilities to be managed. And so some of these early children came to our center.

This is probably the highest performer I've seen from the children we've worked with, and you can see, over time, testing him on this protocol, starting him at about 1 year out to 4 years, and you can see that he progresses nicely. Around the third year follow-up, he's just bordering into open-set, and by 4 years he's just at the lower range of open-set, and he would fall, by 4 years, into the 25th percentile of children with cochlear implants.

Okay. So the 10th percentile group. These are the children that don't progress beyond detection or pattern perception. What about those children? You've got a child who's 8 years old, and you're certainly not going to continue to do the ESP on that child. It's discouraging for the child, and it's discouraging for the parents. So as part of this grant, we developed an auditory/visual test battery, motivated by a clinical need. And these

children are not only research subjects, they're also our clinical patients. It incorporates the closed-set tests, and it emphasizes the multimodal processing.

Okay. So this is just showing you the tests. We did add one test, the NU-CHIPS. All given in auditory/visual condition, all live voice, and closed-set tests. But what's important to know is you can test an auditory only for these tests, and children do have an opportunity to progress, to move back into the standard auditory protocol. And, in fact, after 7, 8 years, there have been some children that do make it back into that protocol. They're just a slower rate of growth.

Right. So also testing in quiet doesn't tell the entire story, so we also have included adverse listening conditions, and here you can see where they're placed in the protocol. So for the Pediatric Speech Intelligibility test, which is a picture-pointing closed-set test of words and sentences, in sentences, we test at a single-talker competition and three different conditions here of +10 message-to-competition, 0 and -10. And at the top, children are tested on Hearing in Noise Test sentences, not only in quiet, but at +10, +5, and 0 signal-to-noise ratio. And you saw, by 5 years, over 75% of the children were in open-set, and soon after that they're topping out. So we need to include more adverse listening conditions.

For the children that do very well in sentences in noise in a fixed condition, we've also included now HINT-C Adaptive, where we can look at the 50% level of signal-to-noise ratio at 50%, and this way we can test really the high-performing children who are unilateral CI users, bimodal, and bilateral.

Okay, I'm going to move to another concept. This is another auditory hierarchy,

pediatric hierarchy, that we were working on around the same time that Wang was working on the SRI-Q, and this is based on a model of perceptual development. It's skill specific rather than test specific. You saw, for an NIH-funded study, multicenter study, you had to have a set protocol, you had to have set tests, and each center had to follow that protocol. But when you're thinking about a clinic, clinicians basically look at the child based on a scale, not necessarily by a test. It's also important to know that tests in vogue 10 years ago may not be as much in vogue today. There are always new tests being developed. So a number of tests can be selected within each skill level and can be applied with different languages.

Am I running out of time? Okay. Well, I'm just going to go quickly over the models. The basic model is of Aslin and Smith on general perceptual development. It was modified by Moeller and Carney for speech perception and production.

And my last slide. We have -- I'm sorry, it's a little difficult to see, but you can see, we have the Aslin and Smith model, the Moeller-Carney model, developmental age, hearing age, and the categories of skill development, hierarchical skill development, under these categories.

And with that, I'll thank you for your attention.

DR. WOODSON: Thank you very much.

Our next speaker will be Dr. René H. Gifford. Please approach the podium. Could you provide copies of those slides to the Panel?

DR. GIFFORD: Absolutely.

DR. WOODSON: Oh, I was talking to the previous speaker.

DR. GIFFORD: Oh, I'm sorry.

DR. WOODSON: But yours too.

DR. GIFFORD: I will too. Yes, absolutely.

DR. WOODSON: Okay, thank you. Identify yourself.

DR. GIFFORD: Yes. Hi, I'm René Gifford. I am an associate professor at Vanderbilt University in Nashville, Tennessee. I'm also the Director of the Cochlear Implant Program at the Vanderbilt Bill Wilkerson Center, in the Department of Hearing and Speech Sciences. Today I'm going to talk about pediatric cochlear implantation: candidacy and outcomes for the non-traditional candidates.

Of course, I want to recognize my disclosures. I am on the audiology advisory board for all three FDA-approved cochlear implant manufacturers.

We're going to talk a little bit about pediatric cochlear implant criteria, which has been discussed a little bit this morning by the Panel. Pediatric implant criteria are currently based primarily on the audiogram and auditory progress of the child, or really lack thereof as far as auditory progress.

The three manufacturers do have slightly different criteria for children, and in particular for one of them, the criteria do vary somewhat based on the age of the child.

The labeled indications, which is important to discuss, really have not been modified for 15 years for children, which clearly is lagging behind the adult indications, which have been modified several times since the year 2000.

This is just a table that outlines the current labeled indications for pediatric cochlear implantation across all three manufacturers. I'm going to just touch upon a few points and

then give some follow-up slides to provide a summary.

But what you're seeing here is we're looking at hearing loss, as far as the three manufacturers go, on the first row, organized by alphabetical order. And you can see that, for all three, they all mention profound sensorineural hearing loss in both ears, with Cochlear also recommending that for children who are over 2 years of age, severe to profound bilateral sensorineural hearing loss would be indicated.

For speech understanding, the degree of disparity is somewhat greater than it is for the hearing loss requirement. All of them outline slightly different measures that can be used for determining candidacy. And some of them, specifically Advanced Bionics, does list an age-specific criterion.

So, for children under 4 years of age, they recommend under 20% correct on a simple open-set test such as the Multisyllabic Lexical Neighborhood Test, or the MLNT. And then, for over 4 years of age, depending on what the clinician decides, if it's developmentally appropriate, you could use open-set words such as PB-K, in which case less than 12% would be the candidacy, or 30% for open-set sentences. The other two have candidacy set in that range as well.

So they define the lack of auditory progress with hearing aids somewhat differently and depending upon the developmental level of the child. So for children who are much younger, who are unable to complete these measures of speech understanding, they define little to no auditory progress, following an appropriate hearing aid trial, as something that a child is not meeting their auditory milestones, say, on the IT-MAIS or the MAIS.

Now, for older children it gets a little bit more complicated, as I mentioned earlier, in

that, for older children, lack of auditory progress is defined by these particular criteria that are outlined by the manufacturers. In other words, I think this is the take-home. Children must miss 70% to 88% of the signal in order to qualify for cochlear implantation, as the current labeled indications stand.

So I'm going to describe a little bit about studies that currently are describing and providing some evidence for the expansion of pediatric cochlear implant criteria. I'm going to highlight this study simply because I was involved with it, so I am familiar with the study. But I'm also going to provide some additional background and additional readings.

So in this Carlson et al. paper, this represented two large academic medical centers, the Mayo Clinic and Vanderbilt University Medical Center. And, specifically, we were looking for children who had been implanted, who specifically were outside the labeled indications for criteria. And our hypothesis was simply that children who are exceeding the labeled indications would derive significant benefit from cochlear implantation either on measures of speech perception testing and/or auditory skill development.

So the inclusion criteria for this study were quite simple. So the children must have been CI recipients prior to the age of 18 years. They did have to have sensorineural hearing loss, and they did have to have bilateral sensorineural hearing loss. So we're not talking about issues with single-sided deafness. These were children who could potentially have asymmetric hearing loss, but the hearing loss was required to be bilateral. Specifically, children had to have a pure-tone average less than 70, or better than 70 dB HL if they were between the ages of 2 and 17 years, to be consistent with Cochlear's recommendation for severe to profound. And they had to have a pure-tone average better than 90 dB HL if they

were under 24 months of age and/or, in many cases, because many of the children met both of these requirements, they had to demonstrate age-appropriate word and/or sentence recognition that was in excess of 30% correct, which we took as the most liberal of the criteria that are currently listed for cochlear implant labeled indications. And these were recorded -- I'm sorry -- derived with recorded stimuli.

Now, our primary outcome measures were somewhat different across children, but what was important was that we used the age-appropriate developmental measure for that particular child and we used the same measure both pre- and postoperatively to obtain our outcomes. And these are just a listing of some of the materials that we used across the children, because obviously we had children ranging in age from infancy all the way up to children who were in their teenage years.

Now, for children who were much too young to even complete any type of even a closed-set test such as the NU-CHIPS, we did use parental questionnaires gauging auditory skill development as a measure of outcomes, such as either the IT-MAIS, MAIS, the LittlEARS, or the PEACH.

So our participants, who were they? There were 51 children across two centers. You can see that the majority of them were implanted unilaterally. The mean age of implantation was 8 years because, of course, these are children that are non-traditional candidates. Many of them had had second, third, and even fourth opinions in order to get a cochlear implant. But the range of implantation was quite broad, ranging from 7 months all the way up to almost 18 years of age. The children, at the time of follow-up, they were experienced users. We did range in age from 2½ all the way up to 46 months of implant

experience, with a mean of 17 months. All were implanted at the time of the manuscript publication with the most recent technology approved by the FDA. And we did have a breakdown with all three manufacturers represented.

Here's the audiometric thresholds, the average and standard deviation for the ear that was to not be implanted, or the non-implanted ear. So you can see that there was a tremendous spread, hence the error bars. But we had children in the non-implanted ear ranging from approximately a mild to moderate sensorineural hearing loss all the way up to profound.

And here is the case, that many of these children had asymmetry in their hearing, which was disqualifying them from actual labeled indications. And so you can see, in the ear that was to be implanted, we were looking more at a severe to profound sensorineural hearing loss.

Now, what we're looking at here are the preoperative speech understanding scores for the children, on average, across all the different measures that were used to determine candidacy. And what you can see here is we have the ear to be implanted, or the ipsilateral ear, in blue, the non-implanted ear, or contralateral ear, in red, and then the binaural best-aided condition in green.

So, as you can see, you can see there is tremendous disparity between the ear that was to be implanted and the contralateral and the best-aided condition. And because the current indications do list best-aided condition, many -- well, all of these children -- but many children today in many clinics are being disqualified from candidacy on this basis, although in an ear to be implanted, they potentially could derive significant benefit.

So here are our outcome slides. So what you're looking at here is percent correct, and it's simply a pre- versus post-implant metric here. And on the left you're looking at speech perception for the implanted ear only, and what you can see is we see a tremendous benefit, with every single child demonstrating a benefit. In other words, no one showed a lack of benefit on this study. And on average, we saw almost a 63-percentage-point improvement across this study population.

Now, focusing here on the right you can see that we're looking at pre- versus postoperative performance in the bimodal condition, or bilateral for those who were bilaterally implanted. And again we're seeing significant improvement with no decrement from improvement, even though some children were already at ceiling because they were doing so well in the non-implanted ear. But on average, we're seeing a 40-percentage-point improvement for these children who would have been disqualified as cochlear implant candidates.

Here are the children that were too young to complete speech understanding performance measures. And so these were our auditory development questionnaires that were simply quantified into a percent correct based on the total number of items that could be listed as correct. And you can see the pre- versus post-cochlear implant scores, and on average we're seeing a 27-percentage-point improvement across this study sample set.

So like I said, there are a number of other studies that have also documented significant benefit for children who are outside the traditional candidacy range for cochlear implantation, and I do encourage you to take a look at these additional studies as well.

But the study conclusions from the Carlson et al. paper were that, one, children who

definitely have considerable residual hearing, particularly those outside of the labeled criteria, do derive a significant benefit from cochlear implantation.

We did conclude also that children who have sensorineural hearing loss, who are making full-time use of appropriately fitted hearing aids, whose parents are complying with the recommended intervention and therapy schedule, but who are not making month-for-month progress in speech and language and auditory skills should be reevaluated frequently and considered a potential cochlear implant candidate because these are the children that fall through the cracks in our clinics.

We also did recommend that there was consideration for a large-scale reassessment of pediatric cochlear implant candidacy in order to allow more children to take advantage of the benefits of cochlear implantation.

Now I'm going to follow up this morning with just a brief mention of implanting children under 12 months of age, which was discussed in some degree this morning. Currently, as we discussed, audiometric criteria are most stringent for our youngest children, profound sensorineural hearing loss, and these are our youngest language learners.

So, currently, for things to consider when discussing whether or not to lower the implantation age, we know that infants are already able to link sound patterns with meaning by 6 months of age, meaning that when they hear the word "mommy" or "daddy" or "bye-bye" or "no," they know what that means by the time they're 6 months.

Word segmentation abilities are developing rapidly from 7½ up to 12, even 13 months of age. Now, word segmentation is the ability to take a string of connected

discourse and pick out the individual words to derive meaning, which is obviously a very important prerequisite for language learning.

Eight-month-old infants already have been shown to be able to store words up to 2 weeks. So, again, this is a very important prerequisite and process in the development of language for children.

There have also been a number of studies that have looked at children who have been specifically implanted under 12 months of age, and these studies have reported significantly better word-learning abilities for those that were implanted under 12 months of age, even when compared with children who are implanted at 13, 14, 15 months of age. There's something about being implanted early to take advantage of these early language-learning opportunities.

Children implanted under 12 months have shown greater and more significant expressive and total language abilities than those implanted at ages that we wouldn't consider old, 18 months of age in some of these cases.

They've also shown higher levels of speech perception when you are able to measure them at 4, 5, and 6 years post-initial activation.

So what we're seeing is that age matters, but our current cochlear implant criteria are strictest for the youngest children.

So my last slide, to conclude, is that the current labeled indications for children are very restrictive as they stand today, with respect to:

- both the severity of the hearing loss, requiring profound sensorineural hearing loss;

- the symmetry, requiring that the degree of the loss be symmetrical;
- age, potentially considering lowering the age because, even though children are going to be implanted at 12, 13 months of age, language learning is occurring before that time and these are all missed opportunities for the child with severe to profound sensorineural hearing loss, and studies have been pouring in showing that this can impact their later outcomes in language abilities;
- and additionally speech understanding, so children are required to miss almost up to 88% of the signal in order to qualify, as the current labeled indications state, and that's in the quiet sound booth, and we know that we don't live in a very quiet world, particularly not children.

So I thank you for your attention this morning.

DR. WOODSON: Thank you very much.

Our third and final guest speaker is Michelle Hughes.

DR. HUGHES: Hi, I'm Michelle Hughes. I'm at Boys Town National Research Hospital in Omaha, Nebraska, and today I'm going to be talking about the use of objective measures with cochlear implants.

Here are my disclosures. Boys Town has been an investigative site for the MED-EL study, the EAS study. The research in my lab is supported by the NIDCD, and all three manufacturers provide equipment on loan for my lab, as well as technical advice. And I'm also a member of the AAA Clinical Practice Guidelines Task Force for Cochlear Implants.

Okay. So when we program or map a speech processor for a CI, it involves a lot of

subjective feedback on the part of the recipient. First we have to get detection of electrical pulse trains, so T-level thresholds, and that's anywhere from 12 to 22 electrodes. Then we have to get most comfortable or upper comfort levels on all of those electrodes as well, and those are defined differently across manufacturers. Then we have to do loudness balancing, pitch ranking, and then subjective preferences or formal speech perception measures in order to be able to compare maps with different parameters, so if you want to try different strategies or stimulation rates.

So what if you can't get that behavioral feedback or what you get is maybe unreliable? Well, one of the benefits that we have is that all of the devices that are out right now, at least the newer ones, use monopolar stimulation, so it's a pretty broad stimulation mode. And the benefit of that is that the levels -- the map levels tend to be more uniform across the electrode array. So that allows us to be able to interpolate and get fewer behavioral responses when it's hard to get them in the first place. The other thing we can do is objective measures, and that's kind of what I'm going to focus on next.

So objective measures can tell us a little bit about device function. It can tell us if the auditory pathway is functioning appropriately, and then it can also give us some guidance in programming when it's difficult to get that behavioral feedback.

So I'm just going to focus on three of the most common objective measures that are used clinically. This is electrode impedance; the electrically evoked compound action potential, or ECAP; and the electrically evoked stapedial reflex threshold, or ESRT.

So electrode impedance is measured via the device's telemetry capabilities, and it tells us if there are any short circuits or open circuits that need to be programmed out of a

device. It also gives us an idea if the device is operating within voltage compliance limits, and it can tell us if there are any atypical impedance patterns.

So some of the consequences of including abnormally functioning electrodes in the maps would be that they can produce non-auditory percepts, poor sound quality. You can get pitch confusions or pitch reversals. And these things can also lead to reduced performance with the device.

Luckily, though, the short and open circuits are pretty easily identified and flagged in the commercial software. So here you just see an example of an open circuit in Cochlear's Custom Sound. So the one electrode with the open circuit is easily identified and flagged here.

And then here's an example of two short circuits in Advanced Bionics' software. So those are indicated in purple, so again very easily identified. And a clinician can just turn those electrodes off.

And then the third example here of three open circuits in MED-EL's software. So again very easily identified.

Out of voltage compliance is a little more tricky. It's a little less straightforward, I guess. So this is based on Ohm's law, where voltage equals current times resistance or impedance. And what that means is that there's not enough voltage to get the current amplitude that's being requested by the user and the software. So if the current pulse amplitude gets to be too large, then we can exceed those voltage compliance limits, and what that means is any further increases in the amplitude really aren't going to be there. So what you can do is just lengthen the pulse duration so the amplitude can be reduced,

and you get the same overall charge and loudness percept and then you can avoid being out of voltage compliance.

Now, voltage compliance isn't always flagged or automatically limited in the software. Here on the left you see an example of a screenshot from Cochlear's software where we've got the T-levels in green and the C-levels in red. And the purple is just the ECAP threshold, so you can ignore that for now. But the red hash marks at the top show you where the voltage compliance limits are. So although they're very clearly identified on the mapping screen, it is possible to still go ahead and set your C-levels above those limits.

Here is a screenshot from MED-EL's software that shows the M-levels here and then the compliance limits over here on the right. But notice that they're in different units. So we've got the M-levels in charge, whereas the compliance limits are in clinical units, so it does take additional steps to kind of convert those.

There was a study by Neuburger et al. in 2009 that talked about stimulating when out of voltage compliance, and it can result in the potential for asymmetric current pulses, insufficient loudness growth, further increases in impedance. And so what they recommended was just simply widening the pulse duration to avoid going out of voltage compliance. And when they did that in that study, then the initial increases that they saw in impedance went back down, so the impedance went back to the normal range.

And then there's also atypical impedance, which is where all of the impedances are within the manufacturer's specified range of normal, but you have a couple of electrodes that kind of stick out as being different from those of the neighboring electrodes. So here are two electrodes here on the left, and then on the right you see those zigzag patterns. So

there's every other electrode in this segment here that has higher impedance relative to its neighbors. So that's just something that requires longitudinal monitoring by the clinician, and clinicians need to be aware of it because it can affect performance at some point.

All right, let's switch gears a little bit to the ECAP. So the ECAP is measured through the device's telemetry capabilities. Basically just a biphasic current pulse is delivered in monopolar mode, and then the ECAP is an aggregate response of the auditory neurons, shown there. It can tell us if the device is functioning, if the auditory nerve is functioning, and in some cases we can even get some information about spatial excitation patterns, and even in some cases potential indications of an electrode fold-over.

ECAPs can also be used to guide with mapping. So this is a procedure that was described by our group about 15 years ago. So with this method you just measure ECAP thresholds on all the electrodes, and then you can just get one single behavioral measure of threshold and then a single behavioral measure of upper comfort. And then you simply just take that ECAP threshold profile, move the whole thing down so that it lines up with that one measured T-level and then move the whole ECAP threshold profile up so that it matches up with the one measure, upper comfort level. And in this case you can see that there's pretty good agreement between the ECAP-based or predicted map levels versus the measured map levels.

But I should also note that that's not the case for everyone. So in some cases the ECAPs don't predict the map profile very well, and so the ECAP threshold profile is shown there in red with the measured map levels shown in black.

Smoorenburg et al. described another way to use ECAP thresholds to program. So in

Step 1, first you measure ECAP thresholds across the whole electrode array and then basically set the map T- and C- or M-levels equal to that and then bring the whole thing down so it's well below where it should be audible and then turn on live voice and then slowly increase the levels where the patient indicates that it seems like they're hearing it. You can lock the T-levels there, uncouple the T's from the C's or M's, and then continue to raise the upper comfort levels until they give some indication that it's comfortable or not comfortable and then you can back it back down.

So important things to understand about the ECAPs is that they almost always fall above behavioral thresholds. So this means that they will represent a current level where the stimulus is audible. So that tells us that we can use that information as a starting point for conditioning young children for behavioral testing, so we know that they can hear it at that level.

The ECAP threshold profile may fall within the map dynamic range, or it can fall above the upper comfort levels. And the two main things that contribute to where the ECAP thresholds fall within the map dynamic range are the stimulation rate, that raising for obtaining the map levels, and then how the upper comfort levels are defined, because again they're defined differently across manufacturers.

So here's just an example of comparing the effects of a slow rate map versus a fast rate map. In this two panels, the ECAP thresholds stay the same because it's a single slow rate stimulus that's being used to elicit those responses. So for the slow rate map, we've got the ECAP thresholds that are actually within the map dynamic range. But as we increase the stimulation rate for the map, then what happens is the T-levels drop due to temporal

integration. We do see some drop in the upper comfort levels, but not near as much as what we see in the T-levels. So, in this example, we started out with a slow rate where the ECAP thresholds are within the dynamic range. But for a faster rate map, now we've got about half of the array where the ECAP thresholds are actually exceeding those upper comfort levels.

And then here's just an example of the different definitions of the upper boundary. So on the left we have MED-EL and Cochlear defining their upper limit as loud but still okay. So in this case the ECAP threshold is going to fall within that dynamic range. But on the right, Advanced Bionics defines their upper limit, their M-levels, as most comfortable. So by definition, M-levels are going to be lower than C- or MED-EL's M-levels. So in this case then, ECAP thresholds are going to exceed the M-levels.

So just switching gears now on to ESRT, or the electrically evoked stapedial reflex threshold, it's similar to the acoustic counterpart. We're just using the implant to provide the stimulus, and the stimulus is the same pulse trains that we use to obtain the map levels.

The research shows a pretty good correlation between ESRTs and upper comfort levels, but they can also overestimate the uncomfortable level. So, again, the upper limit of the dynamic range is defined differently across manufacturers, so that's important to pay attention to.

ESRTs are good to use for young children who are prelingually deafened because they often lack the concept of loud. Oftentimes they will let you sit there and raise the levels until their face is twitching, and you don't want to have that happen, so ESRTs are good to use to kind of bring them back down. They are a little bit more challenging to

measure than the ECAP because the ESRTs do require a healthy middle ear and the recipient has to sit still and maintain a pressurized seal, which is kind of hard for a 1- or 2-year-old. ESRTs are measurable in about 65% to 80% of CI users across studies, whereas the ECAP is measurable in about 95% of CI users.

And then, as far as performance, a couple of studies have looked at speech perception outcomes in adults using ECAP-based maps or ESRT-based maps, and the results show that they do about the same or maybe slightly poorer compared to their behaviorally measured maps. But the take-home message here is that even if they are doing slightly poorer, they're still getting pretty significant open-set speech recognition with these objectively based maps.

So, to conclude, objective measures offer valuable information when the behavioral feedback isn't available or reliable. The predictive ability is not precise, not as precise as we would like it to be, but it can be sufficient enough to provide adequate audibility for speech and language development while children mature and be able to gain those skills to be able to give us more reliable behavioral feedback.

And then there are my references.

Thank you for your time.

DR. WOODSON: Thank you so much.

I'd now like to open the floor for the Panel members to ask questions of our guest speakers, and I'd also like to remind you that the guest speakers will be available to answer questions during the deliberation period too.

Jane.

DR. MADELL: Jane Madell.

Laurie, when you talked about test levels at which you would do testing, quiet and noise, you didn't discuss soft speech, and I just want to say how important I think testing speech perception of soft speech is. We know that children gain more than 80% of what they know by overhearing conversation or incidental learning, so we really need to be sure that kids with hearing loss have that access to soft speech. It's much harder than normal conversation, but I just want -- I mean, do you have any comments on that? I mean, I do think I feel like it's an important thing to add to testing normal conversation in quiet and in noise.

DR. EISENBERG: That's a great idea. You know, for the protocol we did in our study, we tested pretty much across the -- tested at 70 dB SPL, which in 2000-2002 was the standard. After those studies started, people started discussing testing at 50 dB SPL, 60, 65. But by that time we really couldn't change our protocol. Doing it today we would make some changes definitely, especially when you get into speech in competition and speech in noise and especially adaptive testing, you're coming up against head room and compression or P-clipping, whatever the device is. So level is not trivial.

Thanks.

DR. WOODSON: Do you have a question? Okay.

DR. KENNA: Marly Kenna, Children's.

I have a question about the very youngest children who often have tympanostomy tubes in place and whether the objective measures for the non-language based objective measures are actually able to give us enough information to set comfort levels and

threshold levels.

DR. HUGHES: This is Michelle Hughes.

You're not going to be able to get ESRT measures if there's a tube in place, but you can do ECAPs. Does that answer your question?

DR. KENNA: Yes, thank you, I think, since young age is one of our questions and sort of implies that.

DR. HUGHES: Um-hum. And we use the measures routinely for the young kids just because they can't really give you much.

DR. KENNA: Thank you.

DR. WOODSON: Scott.

DR. BRIETZKE: This is a question for Dr. Gifford. Thank you for sharing your study. I really enjoyed hearing it. I just had a question about your thoughts about these results you presented being really the most ideal results possible. You have highly motivated patients, highly motivated parents. They're comparing the child's baseline to their end performance versus probably a more true control group of unimplanted similar children. No doubt that cochlear implants probably are better, but as we apply this to an unselected population, what would you expect the results to be?

DR. GIFFORD: A great question. So there is a study that I am thinking, out of the Colorado initiative for infant hearing screening. I can't remember the exact name. The study that I'm thinking of is Yoshinaga-Itano 2010 where they actually do have a control population, so they have a population of children who were all severe to profound sensorineural hearing loss bilaterally. Then they were either those who went on to get at

least one cochlear implant or those that remained hearing aid users, and the trajectory of language growth was significantly greater in the children that got cochlear implants.

DR. ISHIYAMA: I have a question to Dr. Gifford. I think, just as we already do, it does make sense to lower the age of our cochlear implantation. However, we have to be absolutely sure that these kids who have become candidates don't have any functional hearing remaining. So what is the best -- what is the age limit that you can enforce behavioral testing and you have some understanding that you are doing the right thing?

DR. GIFFORD: That's an excellent question. I can speak for myself, but I know there are those on the Panel that could also speak to this. It's accepted practice in pediatric audiology that by 6 months of age you can get reliable behavioral assessment of hearing, provided the child is typically developing in all other areas, has motoric control of head and neck. I mean, in our clinic, we would feel comfortable once we were able to document hearing status at 6 to 7 months of age in the severe to profound degree. Of course, there's also the issue of neural integrity as well, which is something we haven't necessarily discussed, but I think it's definitely going to be -- it would be something that would be up to the professional clinical judgment of the team. But certainly by 6 to 7 months of age, for a child with motoric head and neck control, you can get behavioral estimates of hearing.

DR. KENNA: Marly Kenna.

I have a question for all three presenters. So as we consider expanding the indications, that will include children who have significant developmental and/or motor delays. Do you think that the language assessments that we have now actually allow us to assess those children both as candidates or post-implant or whether we're going to need

the development of some additional studies? Because I think we're somewhat limited in that patient population by what we can measure.

DR. EISENBERG: So I have several thoughts about this. The first is that, at least for our CDaCI study, there was select criteria for inclusion into the study, and it was based on some developmental screenings, but nevertheless, those screenings don't really catch everything, and after the fact, we thought we had a fairly homogeneous population at inclusion. But then you saw, from our 10th percentile group, that some of those children -- and people often ask, well, what explains that poor performance? We've looked at that and looked at that and looked at that, and it's a whole bag of explanations. One may just be, at the time of the study, we think people weren't -- surgeons weren't recommending the MRIs, so you didn't really see there was absence of auditory nerve.

Today, all the kids get this and they are -- you know, either they're rejected for a cochlear implant because the insurance companies or the funding agencies will not support a cochlear implant if they don't see the anatomy to support that surgery -- and that's when families start seeking now the auditory brainstem implant. Some of the children started showing signs of autism after the fact. So I think that's always going to be a situation. The earlier you go, there are going to be some situations that you just won't know about.

And I will also say, for our pediatric ABI population, almost every single one of those children have come with additional disabilities, cognitive delays, CHARGE syndrome. And so we're dealing with this with all of these children. And not only is testing a challenge, you know, the earliest we're doing the ABI is 2, and these are challenges at 2, just because even programming the device is a challenge when you have these additional disabilities. So I'm

not sure how to answer it in terms of do we need new tests? Do we need new measures? I do think there are measures out there if we look outside of our own field of speech and hearing. We've been using the Vineland skills of daily living -- you know, of adaptive behavior, and we started thinking -- when we started working with children with additional disabilities with cochlear implants, clearly having expectations of speech understanding and spoken language just wasn't going to be realistic for a number of those children. So we started thinking, what is the point of even testing using those markers?

And then we started looking for other metrics outside of the field. Things such as the Vineland scales of adaptive behavior seemed to be a good metric for us. It's certainly validated over and over again, and it's been translated into many languages and used quite a bit with children with autism. And so we just thought, if you have -- and that's also a goal for that child. If that goal is going to improve their quality of life or adaptive behaviors, that might be more realistic than looking at spoken language or open-set speech recognition.

DR. WOODSON: For the transcribers, that was Dr. Laurie Eisenberg. And so for the other two guest speakers, when they answer the question, make sure you state your name before you start speaking.

DR. GIFFORD: Hi, this is René Gifford.

I don't know that I have much to add other than that. I think it's a fantastic topic to discuss. Obviously, I think our expectations will be guarded. And these children tend to be implanted a little later as well, because the documentation of hearing, as we discussed earlier, is going to come at a much later state and sometimes can't come behaviorally either. But then it's more of an issue -- at least for the families that I have worked with, it

becomes more of a quality of life issue, and so our metrics change.

DR. NELSON: Peggy Nelson.

Can I follow up on that with either of you or both? Other than the anatomical markers that you mentioned where you're getting some idea of the anatomy, are there other risk factors or contraindicators that you would say you would not want to provide a cochlear implant for those children with possibly different expectations?

DR. EISENBERG: Well, having been out of the clinic for many years now, I don't have quite the clinical insights. But, you know, we surprisingly are excluding quite a few children, even for the auditory brainstem implant, just because of the nature of the anatomy and additional problems that are associated with whatever occurred during the birth process and prenatally. We just excluded a family for medical reasons, that we didn't think the child would actually be able to probably go through the surgery without tremendous risk. So that's the only one that I could think of at the present time.

I'm Laurie Eisenberg, by the way.

DR. HUGHES: This is Michelle Hughes.

I was just going to add one other thing. So there's the medical risk, but also if the family doesn't seem to have appropriate expectations or proper supports in place, then that would be a pretty big deciding factor. So in these kids with significant developmental delays, just to echo what my colleagues have said, we do tend to use more of the developmental profiles. The DP-3 is one we use, the Mullen scale, the PEDI pediatric developmental inventory. So those are all things that can kind of give you some information about quality of life, and that's really kind of what we hone in on. We also tend

to weigh more heavily on the other caregivers who are involved in the child's care on a more regular basis than what we are as audiologists, so the early interventionists or the deaf educators and, of course, the family, the parents. And we chart things like connectedness to the environment. Is the child alert when they hear their parents speaking? And that alert is different, you know, to have the parents report to you that this child who has basically no cerebral development, that they smile when they hear their dad's voice.

DR. EISENBERG: Or a dog.

DR. HUGHES: Yeah, or a pet.

DR. TOMBLIN: Bruce Tomblin.

One of the indicators across all of the manufacturers also is a hearing aid trial, and none of you have actually spoken to this. But since you come all from very prominent cochlear implant centers, I was wondering the degree to which those trials, particularly with regard to the infants, are employed in any rigorous fashion. What are the criteria that are used to evaluate success or failure on those? It seems to me that there are lots of things that could sort of serve as challenges there and whether in fact that serves as a particularly important part of candidacy in the long run. Anybody can comment on that.

DR. GIFFORD: Hi, René Gifford here.

Well, I think every center might be a little different -- do things a little differently. I'll tell you what we do. Of course, we verify that the hearing aids are providing the target audibility based on the hearing loss for the child. Of course, all children are enrolled in early intervention as well as regular speech-language therapy. We then use both speech

perception measures for infants, so like an infant visual reinforcement infant speech discrimination type of test to see if we can see any changes developmentally, as we would expect, based on the audibility. And, of course, our speech-language pathologists are going to use, like, criterion-referenced tests, even that you can get maybe in that first year of life, looking at auditory skills development, babbling, different types of -- I'm not a speech-language pathologist, but different types of utterances that we should expect to see developmentally. And if a child is not consistently making at least 1 month's progress for 1 month of age over that 3- to 6-month period, then we're going to really start discussing, as a team, whether or not this is a child who is really a cochlear implant candidate.

DR. NORTON: Susan Norton.

So our illustrious speakers are all from high-level academic medical and research centers, and if we support the move to postmarket studies of cochlear implants, these lowered criteria or expanded criteria will apply to all centers, any surgeon who wants to do surgery, and any audiologist who wants to program. And I'm just wondering about the applicability of data obtained in a rigorous academic setting from middle class, upper middle class, highly educated parents to the general population of children with hearing loss and their families and run-of-the-mill -- I mean, your single practitioner, surgeon, and audiologist. Anyone care to comment?

DR. HUGHES: This is Michelle Hughes.

I guess my first thought on that is that that's already going on, the single practitioner doing one implant a year and maybe not necessarily using a team approach. So I don't know that things would change in that regard.

DR. NORTON: But if we expanded the formal criteria, we might have more children who are 6 months of age, 9 months of age, who may even have normal hearing, being implanted.

DR. HUGHES: Do you think that that's maybe already happening?

DR. NORTON: I think maybe your single practitioner is more tied to the FDA, to the 12 -- the standard insurance company --

DR. HUGHES: Do you think so? I don't know, I mean, if the big centers can implant off label like the single practitioner.

DR. WOODSON: We're speculating here.

Sujana.

DR. CHANDRASEKHAR: So just to follow up on expanding criteria. For Dr. Gifford and for all three speakers -- sorry, apparently my Toyota is ready for a pick up.

(Laughter.)

DR. CHANDRASEKHAR: Your slides on Matt Carlson's study showed the expansion of criteria very beautifully, but there was that upper echelon of kids who went from like 95% to 99%, something like that. So I think as we're looking to expand age criteria and hearing loss criteria, is there a way for us to define where an implant is too much? You know, could that 95-percenter have worn a really good hearing aid and not undergone an invasive surgical procedure?

DR. GIFFORD: Um-hum. So that 95-percenter on the data we showed, were those in the bimodal or the best-aided condition? If you look at the ear that was to be implanted, most of them were well below 50% correct. So I think at least my recommendation would

be to really start looking at 8-year specific information rather than a best-aided, because when you have cases of like a high degree of asymmetry across ears, that better ear is going to drive the performance, regardless of whether or not that child is at a disadvantage, because the poor ear is not providing that input.

I would also like to -- if I could just make a point about the previous comment by Dr. Norton, is that I'm in an academic medical center, but I also live in Tennessee, which is a very -- the state has a tremendous amount of poverty. So the majority of children actually that I do see in Tennessee are on public assistance and have state Medicaid. And so I think I don't want there to be the misconception that, because we're at large academic medical centers that have, you know, sort of an air of excellence, the patient population that we see is any different than you might see out in rural communities.

DR. WOODSON: Marly.

DR. KENNA: Marly Kenna.

DR. EISENBERG: This is Laurie Eisenberg.

I just want to reiterate. We're in a similar situation at Los Angeles. The centers that I've been involved with have had a very low SES immigrant population. Two-thirds of our clinical caseloads are usually on public assistance. And I will say, for the CDaCI longitudinal study, that the children were enrolled on case -- you know, consecutively. So as a result, I think the study has a lot of power and generalizability because, between our center, Texas, Miami, you have not only different echelons of socioeconomic status, you also have different ethnicities and race, which gives it a little more power. So, you know, even doing NIH research. Nevertheless, I think the data are generalizable.

DR. NORTON: One question. I seem to remember -- and maybe I'm getting Susan Nittrouer's study confused with yours, but with the need for follow-up, the SES, or surrogate thereof, of the parents was slightly higher than the general population as you reported it.

DR. EISENBERG: I think that was true with our control group, that we -- you know, the control groups were from two centers. One was from a private school, and so that group tended to have higher SES than the cochlear implant sample. But the other control group came from the University of Texas, Dallas, at Callier Center, and they had a much lower SES. So one way that we handled this issue is not only having the two control groups, but most of the tests had developmental norms, and we went to national databases where we could look at our samples compared to national databases.

DR. HUGHES: This is Michelle Hughes.

I just wanted to follow up on something else that Dr. Eisenberg said. Well, so I'm at Boys Town, so that's Nebraska. Everybody knows that's rural, very rural, so we do see a lot of kids with -- we do see a lot of kids that are on Medicaid as well. Just to kind of, I guess, complicate things further, we have a lot of non-native English-speaking children and children growing up in maybe Spanish-speaking homes where the parents don't speak English, but then they get English at school. So just to kind of throw that out there too, that we have -- it complicates the linguistic testing that we can do because they're growing up bilingual and sometimes even trilingual because you're throwing in sign language in there too in some cases.

DR. KENNA: Marly Kenna.

So I have two questions. One is, for the children who are identified a little later -- and we know that age is a factor -- the children who are prelingually or congenitally deaf, and if you identify those kids later, for whatever reason, do people feel that you still have to go through the period of time where they wear hearing aids to see how they're doing? I know that actually is something that we really worry about because now we're making them really old.

And the second is the comment that I had. Within our patient population, we have about 15 different languages spoken at home, and given the Boston area, and we're really interested if there are other studies identified or developed to actually look at some of those things.

Thank you.

DR. EISENBERG: So now I lost my train of thought. What was that first question again?

DR. KENNA: I'm sorry. This is Marly Kenna.

The first question was, if you see a later identified child --

DR. EISENBERG: Right, right.

DR. KENNA: -- why do you really feel that you need to go through the hearing aid trial, because now you're making them older?

DR. EISENBERG: This is Laurie Eisenberg.

And I would say yes, absolutely, just because they were identified late -- they could be identified late for a number of reasons. They just fell through the cracks at a newborn hearing screening, or they didn't pass the newborn hearing screening and then the parents

never followed up, or they came to our country at a later time. But, you know, in many cases the majority of children with severe to profound hearing loss have residual hearing, and it's just a question of what is the functional hearing? What can they do with that hearing? So I don't know any clinic that would not fit a hearing aid.

Now, with an older child, because they have cognitive skills and an attention span that lets you obtain more information from those children, you could really find out very soon how well they're going to be doing with that hearing aid. And really, once you're after age 4, I'm not sure how sensitive that period is, I guess. Are you talking about like 3-year-olds?

DR. KENNA: Well, we often seem to see kids who are 2 --

DR. EISENBERG: Yeah.

DR. KENNA: -- who would have been considered young once, but now we think they're old, and for all the reasons that you just outlined, they come at the age of 2. But we worry that if we're going to delay them, say a 3- to 6-month trial of hearing aids -- and now they're going to be 2½ or they're going to be 3, and we worry about that period where their brain is most plastic. Ironically, if they were 8, although the 8-year-old would hate it, I don't think we'd feel like we were losing as much ground.

DR. EISENBERG: No. Well, I don't think you're losing anything by fitting hearing aids at age 2. In fact, as I say, the majority will have some residual hearing. You're getting stimulation up some of those auditory tracts. It just may not be optimal for speech and understanding speech, but there is some ability for the higher-level maturation with an audible signal, and it gives the child a chance to get used to wearing a sensory device, and it

gives the clinician an idea to see how well the parents work with the child. Will the parents follow through? And I think that's sort of an elephant in the room that we're subtly mentioning, but really it is all about the parents and it is all about the family, and that is in many cases going to make or break the success of this device.

DR. WOODSON: We have -- oh, go ahead.

DR. HUGHES: This is Michelle Hughes.

I just wanted to make another comment about just in regard to the hearing aid trial and in our earlier conversations about potentially lowering the age at implant, in regard to a specific population, and that is the children with connexin 26 mutation. So those are the kids that we know, based on the research, that they do really well with implants, and by having them wait until they're a year old, we're kind of losing a lot of ground with that particular population. So I just thought I'd throw that out there.

DR. ISHIYAMA: Ishiyama again.

I think the question is, how do you define the residual hearing that could be functional when they use their hearing aids? Because, clearly, the data shows that the younger the age of implantation, the better the outcome is. So if you have a child who has some residual hearing but that is not really functional -- and a child of 2 years -- why not implant one ear with an implant and do it bimodal? So the question is, why do we need to cut the line to say keep using the hearing aids?

DR. HUGHES: I'm not sure I quite follow the question.

DR. ISHIYAMA: My question is, if the child has bilateral profound hearing loss -- and we know for certain that the younger the age of implantation, the better the outcome.

DR. HUGHES: Um-hum, um-hum.

DR. ISHIYAMA: So when a child has clear-cut no auditory response, it makes sense to implant those children at the earliest possible time, once we can enforce the behavioral testing as a safeguard. Now, we have another class of children who may have some residual hearing, but we know the kid is going to probably do better with the implants rather than enforcing the continued use of hearing aids. So I think it's critical to know, yes, the child has some residual hearing, but rather than enforcing hearing aids for 3 months, 6 months, why not draw some kind of objective data to say, if the diagnostic criteria is so-and-so, by what age do the implant?

DR. HUGHES: Are you talking about separating out bimodal versus bilateral implantation in kids with residual hearing?

DR. ISHIYAMA: When the kid has bilateral profound hearing loss with some residual and then -- I don't know what the cutoff parameter is going to be. I think that's something that we're going to discuss this afternoon. Why not implant one side with a CI and do bimodal?

DR. HUGHES: If they're profound though -- I don't know. René, you can probably weigh in. She's more of the bimodal expert than I am. I'll let René answer that one.

DR. GIFFORD: René Gifford.

I think we do. So I think that you're absolutely right. So we have a child -- so I'll tell you my clinical experience and my opinion is that if a child has severe to profound hearing loss that's been documented behaviorally and objectively, I'm absolutely going to recommend a cochlear implant because the data are pretty clear that we're not going to get

the speech sounds necessary for language development and speech production that that child needs with current hearing aid technology and with the physiology and what's going on within that auditory system. So I'm absolutely going to recommend an implant. We are almost always going to do sequential implantation anyway, so we're going to see how the child would do bimodally and then recommend a second, if the child -- again, this is a whole other question. You know, how do you determine bilateral versus bimodal? But, absolutely, I believe that there's probably a criterion based on hearing loss that we could just say we know this child will do better with the cochlear implant than with current hearing aids. And I think that's one of the things that's meant to be discussed by the Panel.

DR. WOODSON: We have about 15 -- well, actually, it's getting closer to 10 minutes before we break for lunch, and I want to remind the Panel members, you shouldn't really be discussing this issue during lunch. So I'd like to have a few minutes now for us to hear from each other, and I'd like to go around the table and just hear, in a few sentences from each of us, kind of where you think the major issues in your mind are with regard to this premarket to postmarket shift in the data requirements.

So we'll start with Jane.

DR. MADELL: Jane Madell.

Okay. So I think we had very good information this morning and the areas that I'm thinking about right now are age of implantation. I think it needs to be lowered.

I think the question of how do you know whether a hearing is not working is a very important one. In my clinical experience, what we do is we get aided thresholds. I know that's not popular anymore, but it actually tells us something. If you've got aided

thresholds at 40 dB, you know this kid is not hearing well enough. If you've got aided thresholds at 25, well, this kid is hearing well.

And the length of hearing aid trial, in my point of view, is an issue we have to discuss. As long as we know that the child -- if we're absolutely sure the child is not benefiting from a hearing aid, I don't know that we have to beat a dead horse, as it were.

I strongly think we need to look at implanting each ear -- evaluating each ear separately. A child may have a moderately severe hearing loss in one ear, but the data is very clear about the advantage of bilateral hearing, and we need to look at each ear alone.

So degree of hearing loss, age at implantation, each ear separately, how long you need the hearing aid trial, and adding soft speech as a way of looking at performance, I think, are all critical.

DR. WOODSON: Dr. Nelson.

DR. NELSON: I'm trying to frame my thinking in terms of the premarket/postmarket shift kind of context. So I'm not --

DR. WOODSON: You're not totally constrained.

DR. NELSON: Oh, okay. All right, very good. So I think we've raised some really interesting questions. I'd just like to remind, I think, many on the Panel, there are ways of measuring auditory function at very young ages. So I think we can get more specific about recommendations that we could use or best practices or such things so that we can do that kind of evaluation maybe on an ear-by-ear basis for auditory input and output and growth in a short period of time. So I think we want to think about that as well. And -- yeah.

DR. KENNA: This is Marly Kenna.

I agree with the two previous speakers. I'm thinking about the premarket to postmarket and whether we can use the adult data. I think we can probably extrapolate a lot of the safety and some of the efficacy data, which has been beautifully collected and very well documented.

I think that, as we were just talking about, the time with a hearing aid, a well-fitted hearing aid, and speech-language therapy before the child goes on to a cochlear implant is obviously open for discussion. I think there's a lot that we do not know for which we do not really have older child or adult data which includes single-sided deafness and the non-traditional patients, although that beautiful presentation will certainly be helpful. So I think that's data that we don't have that we would need to collect. How we do that and so forth, I think, needs to be discussed.

Thank you.

DR. TERRIS: Dave Terris.

I would say, with now almost 100,000 implants being accomplished with good safety and efficacy data, it seems very reasonable to shift to postmarket assessment.

DR. NORTON: Susan Norton.

I would agree with the previous speakers, but with a couple of issues that need to be addressed, and one of them is manufacturer implementation of speech processing strategies as defaults where we know, for young children, overhearing is very important. For instance, Cochlear now has a default called scan, that introduces directionality automatically. This is not appropriate for young children learning language and needing to overhear. And there are other things like that where, in the hands of less non-pediatric

clinicians, result in limiting access to auditory information. And so that needs to be addressed in terms of how speech processing and programming software to be applied to pediatric population is implemented by the manufacturers and maybe getting into the issue of defaults.

The other thing is the influence of parental compliance on the decision to implant and the age to implant. It doesn't do any good to subject a child to major surgery and then not have the parent comply with the use of the device and the necessary follow-up to optimize access to auditory information with that device. And certainly parental ability to comply is something that is a problem now. It's also a problem for all of pediatric, for all of medicine and my colleagues in transplant and oncology. We're actually having a conference, a bioethics conference, on that topic.

And then addressing the issue of anatomic limitations and also addressing the issue of the immune status and how we address the issue of non-vaccinators in implanting young children.

DR. WOODSON: Thank you.

DR. ISHIYAMA: I think most of the issues have been already discussed. I do agree that we can shift the majority of the issues to the postmarketing from the premarket. I think you have already addressed all the major issues that we are going to be discussing this afternoon, but there are a couple other issues that I think still requires a little bit of a clarification.

In California, unless you are affiliated with a major medical center, the reliability of a newborn testing hearing is very sketchy. So I want to know what could be done to make

sure that the newborn screening test accurately produces patients who need help. And also we see a lot of situations where the follow-up is a problem where, by the time the patient gets referred to us, there is a substantial delay in diagnosis. And those are the issues that I think we want to clarify.

And, lastly, if you look at the cochlear implantation criteria at the state level from the CCS, which is the California Children Services, their diagnostic and approval criteria is drastically different from what's been written for the FDA criteria. So I think those are issues that we want to talk about this afternoon.

DR. BRIETZKE: This is Scott Brietzke.

I agree, there's a strong case to shift to postmarket analysis. However, it was mentioned earlier about a tiered approach depending on the type of question. I think we'll certainly want to consider that later.

And one just quick comment. We've heard a lot of enthusiasm from audiology to move the age limit lower for implantation, with good reason. Just from the surgery side of things, I think there would be an inevitable increase in complications just from the skin thickness alone on a young child and their immune system still developing. That could be expected. Probably not enough to make it still the right decision, but it would be something that would have to be factored in.

DR. WOODSON: Thanks.

Dr. Tomblin.

DR. TOMBLIN: I think most of the thoughts that I've had, I've heard already. I guess the lingering issue that I have is if we do -- and it seems as though there may be good

reason to consider dropping the severity of the hearing loss some, but I guess then the question becomes how low to go. And I guess, in my mind, I think that the edge is always to acoustic hearing over electrical hearing where that's possible certainly. And I guess, in that regard, we have to consider the fact that acoustic hearing works a lot better for music and other things. We can't be so speech centered that that's the only kind of auditory experience that we prize.

So then it becomes one of a contest at certain points of where is it that the hearing aid gives maybe better overall benefit than the cochlear implant? And that may ask for a kind of study that literally pits those two devices, and there aren't very many of those. And, in fact, I've tried to do them, and they're hard. But I think that's -- and I particularly think about this with regard to dropping the age as well, because then it becomes harder to have confidence in how much preserved hearing there is and so forth. It's sort of at the edges of the issue, but I think we really have to contend with things.

DR. WOODSON: Thanks.

Dr. Houston.

DR. HOUSTON: The issue of using adult and older child data to inform younger children, I'd never really even thought of that question before. As somebody who studied infant speech perception and early language development for almost 25 years, my initial reaction is, no way. And in this particular case these populations are very different. You have one population that's postlingually deaf, so they already have a language system built on acoustic hearing that then they can map onto the electric hearing. The other population is learning language from this electric hearing from the cochlear implant.

Okay. But then I've been thinking about this a lot over the last couple days. The thing is, is that when we're talking about these modifications, right, with cochlear implants and processing strategies, these are all relative to natural hearing, acoustic hearing. So you have acoustic hearing over here, right, and cochlear implant electrical hearing over here. These modifications are changes of this degree, and they're all relative to natural hearing being way over here. And the fact that infants and children are able to learn language from this electrical hearing tells us it's really -- I mean, cochlear implants are remarkable. What's really remarkable is that the human brain is able to adapt to the signal. So we already know that infants can learn language well with highly degraded information.

So changing how this highly degraded information -- exactly how it's highly degraded -- I think the risk that changing that if it produces a benefit or at least doesn't make language processing worse in adults, the chances that it's going to make language processing worse in infants is exceedingly small, so small that really I think it calls for moving it to postmarket.

DR. WOODSON: Thank you.

Sujana.

DR. CHANDRASEKHAR: Sujana Chandrasekhar.

I agree with actually all of the speakers, including your "I voted yes before I voted no."

(Laughter.)

DR. CHANDRASEKHAR: I feel sort of like sitting next to John Kerry. It's all good.

(Laughter.)

DR. CHANDRASEKHAR: But I agree with all of the speakers, and I think you're right, it's a little counterintuitive, but in fact, it's what we've been doing all along. I think that the processing and programming strategies that have been adjusted in clinical use by our speakers and by many of the people around this table have already started to address that in a very effective manner.

In terms of waterproofing, I think children need waterproofing more than adults need waterproofing. I remember taking my kids out sledding 10 or 12 years ago, and there was a mom signing to her child up the hill, and I said, oh, how come you haven't thought about a cochlear implant for your kid? And she said, oh, he's got a cochlear implant, but he can't expose it to the snow. So she had to keep signing to him when they were in snow sports, so it's not just for swimming.

I think, in terms of expansion of indications, we have heard very good data here and at a series of pediatric cochlear implant meetings and presentations that we need to look at expanding criteria in terms of severity, in terms of age of implantation, and also to look at bilateral or bimodal implantation for maximum speech and language and educational benefit.

I agree with Dr. Kenna that there's not enough data yet in adults or children for single-sided sensorineural hearing loss and cochlear implantations.

I think that the test metrics for younger children has been discussed very nicely, and I think if we can incorporate that, that can actually go to communities where maybe it's not a pediatric audiologist or a pediatric cochlear implant audiologist, but in fact somebody who can maybe benefit from telemedicine, as was presented at the very beginning, for help with

this. But we can certainly get this technology to more people in areas where they don't have to travel long distances for big centers.

DR. WOODSON: Thanks.

Dr. Hirsch.

DR. HIRSCH: Barry Hirsch.

As I mentioned before, I think a lot of the devices, and especially the software, are being used off label already. So when I looked at the packet that we received and reviewed it, it seemed like a no-brainer to say, well, why wouldn't you take new technology and apply it to kids? So the question that comes up is, is it unsafe? Is there a risk in doing that kind of technology to kids? And I don't see how there's a safety issue. Unless there's some kind of electrical stimulation that's going on that would hurt a kid, it shouldn't be any risk.

But the next question is -- obviously, that you've been trying to talk about -- what's the benefit? What's the efficacy? In other words, what's the outcome? So it really makes sense that we extrapolate postmarket stuff and put it to premarket and then look forward. After you implant these kids, how are they doing? So I'm going to put a push for postmarket studies that have to follow these things over time and not just say, oh, we'll report it. It really should be a formal reporting.

Sujana just mentioned about single-sided deafness. There, I would not extrapolate adult to kids because there's no adult data yet about single-sided deafness as yet. So how could you even talk about a cochlear implant in a single-sided deaf kid just yet? So we've got to see what it does to adults. It probably would help, but who knows? When you have a normal hearing ear and the other ear is getting electrical signals, you really don't know --

even though there's great plasticity, you really don't know how the brain is going to handle that.

DR. WOODSON: Well, thank you.

I think now it's time to break for lunch, and we'll come back at 1 o'clock to start the public portion of the program. Oh, actually, we have one more announcement here.

LCDR GARCIA: Before we break for lunch, if there are any public speakers that have registered prior to this meeting today, please come and see me before you go to lunch. I want to make sure that you're here so that when we call out your name, you're here and that we're not calling a name for someone that's not here.

Thank you. Enjoy your lunch.

DR. WOODSON: And, Panel members, don't leave any of the material on the table, and remember, you're not supposed to discuss these issues during lunch.

(Whereupon, at 12:06 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:02 p.m.)

DR. WOODSON: We'll now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Lieutenant Commander Garcia will now read the Open Public Hearing disclosure process statement.

LCDR GARCIA: Thank you, Dr. Woodson.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Thank you very much, Dr. Woodson.

DR. WOODSON: Thank you.

There have been five advance requests to speak publicly. Do you have an update on the list? So we have three people here that are going to speak. We'll start out with Mr. Sean Bundy. Would you please approach the podium? You have 10 minutes to speak.

MR. BUNDY: Thank you. My name is Sean Bundy. I'm the Director of Regulatory Strategy for Cochlear Americas. I am a full-time employee of Cochlear, and they paid for my travel and attendance at the meeting today.

First of all, I want to acknowledge the work that the Panel is doing here and thank you for your participation in this process. This is a very important meeting, and it's a very important topic, and the work that you're doing and the input that you have is extremely valuable to us, to the Agency, and helps move the industry forward, and I'm just very grateful for that. I'd also like to thank the Agency for recognizing the need for this discussion and for setting up the Panel meeting, getting the Panel meeting together and coming up with the topics, and helping to move us forward in getting access to technology to American citizens, to this technology faster.

So the focus of the remarks today -- you guys have been drowning in data so far, so I'm going to try not to drown you in any more data. We'd really like to focus on the trial construct. Some of the questions that you're facing are focusing on the appropriate construct of trials, whether they be premarket or postmarket. So I'll talk about what a good trial means in terms of generating data that's appropriate to the technology and the research in question, what study populations we should be looking at, some appropriate endpoints, and then also share some of the experience from our past post-approval studies, as has been referenced earlier in some of the Agency's presentations. And then also just go

after the impact of some of the restrictive indications. What does it mean when we get an indication that's for 6 years old and above? What practically does that do?

So from a trial design standpoint, as we heard this morning in the Agency's presentation, the innovation comes in many forms. There's electric-acoustic stimulation, acoustic signal processing. It was a good presentation this morning lining out the different areas of technological advancement, from very minor changes in acoustic signal processing all the way up to very novel approaches in electrical stimulation and electrode design. And what's important is that if we're going to design a good study, we need to generate data that's appropriate to the question at hand. So we need the right type of data, we need it in the right type of subject, and we need it at the right amount of time. Otherwise we are not executing an effective study.

So what is the right type of data in the context of one of these studies? There is certain functionality that can be demonstrated entirely on the bench, things like a wind noise reduction algorithm. You can present an intended signal and record the output of the device. You can present the signal in the presence of the interfering noise source and record the output, and then you can see the output of the device when the wind noise reduction algorithm is in place.

Now, having conducted clinical trials trying to estimate the effectiveness of wind noise reduction, I can tell you it's really difficult, first of all, to find windy sound booths. They don't make too many of those. And then, secondly, the testing is in a very controlled situation, and the intent of some of these changes is for a very specific listening environment that doesn't lend itself very well to testing in those very controlled

environments. So there are some technologies that are better suited for bench testing than they are for clinical testing.

We also need to give consideration to the existing literature. And we've heard a lot of great research today, good studies that have been published. And one of the ethical concerns with research is that new research shouldn't unnecessarily duplicate existing knowledge, and there are times where industry -- the clinicians have moved so far beyond us in industry that for us to run a pivotal study for some areas would be unnecessarily duplicating some of this information. So while individual studies and small groups of studies may be subject to publication bias, as the Agency has noted, there are also possibilities to do meta-analyses of areas where a large amount of research exists and draw meaningful scientific data from that. And we think that should be considered.

For minor modifications to existing technologies, as we have been discussing, this shift to postmarket data seems very appropriate.

So the fundamental question that you'll probably be facing later today is what the threshold is. Where should we draw the line between premarket and postmarket data? And what we would say is when that fundamental risk-benefit question is no longer the same, when the basis for that determination of safety and effectiveness changes, we need to establish new clinical data, premarket, in order to answer those questions.

So then we come to the subject. Who is the right subject for a clinical trial? Everybody has mentioned today that there are significant problems sometimes in trying to gather very discrete data in very young subjects. The test measures that we have for kids, especially under 24 months, just really are not adequate for very granular changes in

speech performance. And the developmental measures that we have, even if we intended to do a very long-term study for 3 years or 4 years, these outcomes can be very much confounded by so many other factors, socioeconomic status, habilitation setting, the skill of the surgeon, frequency of visits and outcome -- it's very effective in determining the efficacy of cochlear implantation of the intervention as a whole.

But when we start talking about a minor change in a speech-coding strategy, the addition of a new speech-coding strategy, trying to take those measures over the long term in these subjects doesn't generate a lot of meaningful data. It's not capable of showing benefit, if it exists. And, conversely, it may not be capable of showing a detriment, if it exists, in those patients because the granularity of the data is just not at a fine enough resolution to be able to detect the changes.

So the best data really come from the best reporters when we're looking at some of these small changes. And the materials that we have available for adults are much more capable of detecting small differences in performance, small changes in outcomes, and telling us more about how the technology is working in the intended patient population.

And for some of these changes as well, the reliability of the self-reported outcomes becomes critical for questions like instant learning. Do we know if one of these noise reduction algorithms is too extreme and is crunching too much sound? The only way we're going to find that out is going into a patient population where we can actually detect those sort of issues. And, for us, the adult population is probably more able to provide that data than the pediatric population.

And as has been mentioned before, if we can show benefit, if we can show that the

technology works and is not concerning in an adult population, we have no reason to believe that that will be any different in the pediatric population. Now, there are areas of concern that we need to address and keep in mind because these are patients who are still developing speech and language abilities. They weren't postlingually deafened. They were prelingually deafened, so we need to be sensitive to those sorts of things. But I think the data that we can gather from an adult population may be more capable of showing us what those areas of concern are than trying to execute a very long study in a large population of young kids where we don't know what the data means.

So that raises the question of the right amount of time. For some of these changes, acute data should be adequate to show that the technology works and works as intended. Some of the directionality settings, minor changes to coding strategies, something like the wind noise reduction algorithm, we don't need a lot of longitudinal data in order to demonstrate that these things are effective. There's not a washout period that's required for the previous therapy to now leave the patient. As soon as you switch over from one strategy to another, the acute data is actually more of a worst case because the patient hasn't had the time to adapt to the new stimulation that they're receiving. So if we can show effectiveness in the short term, it's very likely to be effective in the long term as well.

And prior studies show that the significant changes occur very early on. This is taken from our adult Freedom postmarket study, and the most change that we saw in the patients was between the preop interval and the 1-month post-activation interval. And while they do tend to perform better over time, you can assess the effectiveness of some of these interventions very early on in the process. So the need for a 6- or a 12-month interval, from

an efficacy standpoint depending on the type of technology we're talking about, it may not be necessary.

And that said, there are inherent disadvantages to very long studies. Subject recruitment can be very difficult if the subjects know they're going to have to participate in the study for 4 or 5 years. Retention is lower in these studies because these patients -- this isn't an oncology study where they're going to the same oncologist in order to stay alive. These patients move. You know, they go from one side of the country to the other. They decide to change clinics, and we can't compel them to stay in the studies longer than they want to. It also becomes difficult for the clinics to commit.

So what have we learned at Cochlear from our post-approval experience? I think one of the things we've learned is that there are different designs for post-approval studies, and what might be appropriate for the Hybrid study, being a 5-year study of 100 subjects with an expectation of 80% follow-up, which if we execute it successfully would be the longest, largest study that's ever been done by a cochlear implant manufacturer -- that's not appropriate for all the types of changes that we're discussing. There could be smaller, more acute studies that would be appropriate.

The pediatric postmarket study that's been referenced previously by the Agency and has been discussed, we had a 12-month endpoint, but it took us 4 years to execute that study, and that was because of the difficulties that we mentioned in recruiting patients and finding sites that were interested in participating. And subject retention was extraordinarily difficult in that study, especially since most of the subjects we were studying were very young. Sixty-eight percent of the subjects in that trial were under the age of 2, so it was

difficult to get them to come back on a routine basis for routine follow-up appointments.

In addition, the IT-MAIS was the only outcome measure that we had, and you're looking at an intervention that takes you from a score of about 10 to a score of about 30. And so the incremental changes in that were very difficult to show. We didn't see any significant differences among the different rates that we were studying, and the adult data that we gathered from the Freedom study actually allowed us to draw a lot more conclusions about the importance of the rates than the pediatric data did.

And although it was successfully executed, we did update the labeling. The fact of the matter is, the labeling was updated 5 years after the product was approved, and the next generation of implant and processor was already available on the market. And so if the period of collecting this data goes too long, if the intention is for us to update the labeling, then the period of the study needs to be such that we can do that in a timely manner and it's still relevant to the products that are on the market.

So why are we here and why do we care? Really, the problem with restrictive indications -- and I see I'm running out of time, so I'll try and do this quickly -- is that, as we've heard today, we use these products off label frequently. The indication doesn't necessarily limit the use of the device in the market, but what this does do is it limits our ability to answer questions from clinicians when they call us. If somebody asks us a question about an off-label use of the product, we're reluctant, as clinicians, to say no, you can't do that. And we're also reluctant to say yes, you can do that and here's how, because of fears of off-label promotion.

So out of time. I'll thank you guys very much for your attention and for considering

this. Thank you.

DR. WOODSON: Thank you very much.

Our next speaker is Dr. Ilona Anderson.

DR. ANDERSON: Good afternoon, ladies and gentlemen. I'm presenting MED-EL's perspective on assessment in children. In 10 minutes we can't cover everything, unlike if I was the FDA and had this morning, so we're just going to take a snapshot on what we have.

I have three authors on this paper. I have worked at a number of clinics before moving to the University of the Witwatersrand in Johannesburg, South Africa, to teach audiology, where I joined the cochlear implant program there. Fourteen years ago I moved to MED-EL, where I'm now the Director of Clinical Research.

Peter Nopp is Director of Research-Signal Processing and has worked at MED-EL for 20 years, and his background is in electronic engineering. And Fritz Ender is Director of Regulatory Affairs and Quality Assurance. He has 25 years experience in the medical device field and has been at MED-EL for 3 years.

This is our mission, just to highlight who we are. But really our key thing is to work on communication and to improve quality of life, and that's the heart and core of MED-EL.

Now, the ISO 14155:2011 is the guideline that drives our clinical research. It's not been mentioned today, but it's what we have to follow when we do a clinical study. Now, the interesting thing on page 7 -- and its amidst a lot of definitions -- is that a child is considered as part of a vulnerable population. And I know you did mention that in the Executive Summary, but I'd like to highlight that because it brings with it many, many things, and that we should only really carry out studies in vulnerable populations when they

cannot be carried out in non-vulnerable populations. And perhaps that is something we need to think about as one of our arguments of what we do with our children, and that really any of these studies should address health problems and that should offer direct health-related benefit to that vulnerable population. So I just want to lay that out there, and that's what's impacted on what we are doing at MED-EL.

And we have concerns about what we're doing, and one of those: Can we ethically put children into classical study design? And I think it's a little bit what Sean was saying as well. In a true study design, you're going to have a static study group, and that might be a problem. Such studies would also reduce our treatment options, and this makes it quite difficult in two aspects: you may take a treatment option away from the child if they have to be in one specific group, and too, you take the child to the audiologist, who follows that child. And I think that's key in our field, is that these children are followed, except if they run away. And we want to -- so we take that chance away for them to be able to decide what is the best treatment for that child if they sit within a static study group.

Again, the duration of the study. Even though the endpoints might be short, it's often very difficult to recruit, and we also don't want to be finishing a study when we already have a new product on the market.

And then there are other things here: language development, cognitive development, and motoric development. All of these are interlinked. When we assess auditory development, we are assessing these as well. They impact on who can and can't do what test metric we choose.

And then I think one of the other things that we need to address is that 40% of

children with hearing loss have additional needs. Some of these are quite subtle, and they're only picked up later. So even if we had a strict study criteria, we may not have identified these at the time of the study start, okay, and so that means we have not a very closed group of children.

If we had a look at how the FDA laid out their questions, the first thing we see is device modifications and change in indication. And we think the list you have there is really an excellent start, and I'm not sure I would take anything off that list. Prioritizing? Maybe, yes. Waiting for more data? Maybe, yes. But I think we also need to think about it shouldn't be an inclusive list. What comes up next year we don't know about. Or the following year. So when you discuss this as a group, I think we would like to think about that. I'm okay if you prioritize, but let's think about not making it completely closed.

If we extrapolate data from one group to another, we need to think about more -- okay. So we believe in using adult data. And I'm going to say adult data because I think, with the older pediatrics, they are the difficult group to recruit. Okay. Often there are additional needs and there are other things that they haven't got there. And yes, some of them are postlingual, some of them are progressive, but they're not the easiest group to get together, so we would use adults there.

But we think we should rather be dividing our children into pre- and postlingually deafened children rather than 2 to 4 or 4 to 6 or something like that. I think that has a greater impact on what we're talking about here. So for postlingually deafened children, yes, use adult data.

But what about prelingually deafened children? Well, the key is, if you're a 19-year-

old prelingually deaf child who got implanted at 1, do you have the same restriction? We need to think about that, the same restriction as if I'm starting with someone who's 2 years old of age. So we would also use adult data. And I think we need to think, if you're a parent of a young child, would you really want flexibility of fitting so that the audiologist can choose the right data? Or do I restrict my child into a very specific study design? To our knowledge, all the innovations that have benefited adults have translated into children so far.

What about the relevance of data? We think that any data provided should be fit for purpose, be relevant to the population, and should follow a well-designed clinical protocol. And if you do that, then there should be good data. And this should be considered scientifically and clinically relevant. And just to say that there is the new OUS guideline that does drive for what we do.

So to post-approval studies, one of the things that I think is we shouldn't define what tests we use as an essential test today because what is essential depends on the question we're asking. So the purpose defines the metric. Okay. So a test that I might be doing to look at age at implantation or degree of hearing loss may be different from a test that I'm looking at wind noise in my very windy test booth. And I think also the outcome domains we decide on are governed by the purpose of what is being measured. So I wouldn't like to really put a pin on it completely. And I think the endpoint is also bound by what is being tested, and this could be up to 1 year with follow-up, but it does depend on what you're asking.

So we had some ideas about what would be a measure, because that is one of the

questions, and we thought you could run a more generic test method. So we have the Auditory Skills Checklist. This was developed by MED-EL because the statistician at FDA asked for something at the time when we were getting our original approval in the U.S. And this is quite a generic thing, but it starts from very basic listening to very more explicit listening, conversations, and noise. So you can follow the children over time.

We also have the LittlEARS Auditory Questionnaire, which someone mentioned before, and that would be if we were testing very young children.

But depending on what we're doing, we may also do something like use a test battery. And I know that this is what one of the speakers was saying earlier, that we need to have a hierarchical measure of tests because the children start off quite young, but as they grow -- because, remember, with language and commission and everything else impacting, they're able to do more difficult tests.

This is an example from the EARS study. We had 726 children in the study over 12 years. Yeah. And we were able to say that on a graph, and I have a copy here. It is available on the MED-EL website if you use this, but I've picked the MAIS because I think that is quite a commonly used measure. You can choose the age that the child is implanted and see on average what they would get on this graph. So if you were implanted between 3 to 4 years of age, at preop we've got 10%, nothing at first fitting, 40 at 1 month, 62 at 3 months, 72 at 6 months. And these graphs actually go out -- I've got 19 seconds -- to 5 years. And they can give a good idea if children are following a standard curve of what happens. That's the highlight, that as you get older, there are fewer children. Okay. And it also says that the very young children aren't really able to perform on this task.

We also want to highlight the idea of doing a study specific registry. So not a national registry because, although it's a good idea, I can see getting data in for that as a nightmare, but rather to choose a registry that answers a question. In this way, you get more basic data, it's more clinically related, and it also helps with the least burdensome approach that we believe in following.

And with that, I'd like to thank you.

DR. WOODSON: I'd like to thank the public speakers.

Does anyone on the Panel have any questions for any of these -- oh, okay, we have one more. Sorry, Dr. Navarro, I'm jumping ahead. You're the last one. Okay.

MR. NAVARRO: Good afternoon. My name is Cedric Navarro. I'm the Global Vice President for Regulatory Affairs and Clinical Research at Advanced Bionics. I'd like to thank the Panel members for being here today. I know we all have busy schedules. I appreciate all your valuable input this morning, and I thank you, FDA, for adding this second day to the Panel meeting.

But I'd like to start off with just some comments that were made this morning about reliability reporting and metrics and standard of care. I am the chairperson for the AAMI committee for U.S. cochlear implants. If any of you are interested, that document will be going out for public ballot in approximately 2 weeks. Love to get any of your feedback and input, and I can provide you a copy in advance of that ballot if you're interested.

In terms of premarket considerations, really what we're looking at is the safety and efficacy of the implant system design and what new or additional claims are going to be made by any feature or product change. Today, amongst all three manufacturers, our

system architectures are pretty identical. And what that means on the good news for our recipients is that the safety and efficacy risks are well known and characterized.

So when we're looking at the adult versus pediatric considerations to look at moving to postmarket, it's important to know that in terms of safety, the major safety issues deal with electrical safety, charge balanced stimulation, charge density limits. None of those are affected by shifting to adult data. And, in fact, over the years, FDA has been pushing industry to come out with software that actually has lower charge density limits, so all of our software that we use today for stimulation is inherently safer by having a lower potential charge density.

There are two known risk factors which are affected between the pediatric and adult indication. One is for external components, for long cables, for lanyards, issues of strangulation and choking. Those are already addressed by design and by labeling. And then we have the case of bacterial meningitis that's already addressed by CDC recommendations. So if we look at the shift to adult data just purely from a safety perspective, there are no other considerations that we should be worried about.

In terms of efficacy and the list that was presented by FDA, what I would state is this, is that for external hardware physical design, all of that can be confirmed by bench data. There would be no need for postmarket or clinical data for any form factor change.

When we look at the design of a new implant or a change to the implant, I would believe that in most cases adult or other postmarket data sources would be a viable option. So, again, that's using the same claims. If we're going to change a surgical technique or make a drastic change, of course, we would need to do some type of clinical data. The

other key areas are where we're making algorithm or mapping changes. In this case, too, I would postulate that the use of adult or other postmarket data sources would be a viable option.

The last part, where all the manufacturers are working on now, is we have devices where our patients have a ceiling effect. So we've got to come up with harder test measures focused on performance and noise in a real-world environment. What we're trying to do is make the cochlear implant experience easier, reduce fatigue, improve the quality of life, so we're introducing a lot of front-end audio signal enhancement features.

What noise seems to be popular today? A lot of these features can be fully confirmed on the bench. You can listen to the output of the algorithm as a normal hearing individual. So I would postulate that all of these could be confirmed by bench data and, if required, supplemented by a postmarket data source.

What I've shown here is just kind of a view of how the system architecture looks, and what I wanted to show is when we're looking at safety, it's about charge balanced stimulation in the implant, and it's about the algorithm that we use to do the spectral analysis and the mapping.

These are the constituents here that affect, for example, the learning and rehabilitation for the brain having to learn how to interpret this new signal.
But when we look at whether it's a beamformer, which is a hardware platform, or front-end processing, these features here are completely independent of the learning process of the electrical stimulation and safety, which is why I stated that these should be able to be fully proven via bench data.

I'm going to talk now about postmarket data considerations. So both Sean and Ilona have talked about the postmarket. Where I actually want to take a shift is look at the CDaCI study. There are many multiple options, and for me, the CDaCI study, why it has this value is this study has been going on since 2002.

There are 188 CI recipients from 6 U.S. centers; 97 normal hearing peers in the control group. The assessments were made at baseline, every 6 months, and 1 year annually after that, after the first 3 years. The study is still going. They are now collecting data 8 years of following these patients. The domains that were assessed were language development, speech recognition, cognition, psychosocial/behavioral development, and quality of life. This is a very powerful, truly randomized study that has recipients from all three manufacturers.

What's impressive about this study -- and I don't want to have anything inflammatory. So there actually is a data point for children implanted off label but below 12 months and I took off the slide. But what's important to look at is, this gray line here is for your normal hearing population, and you can look at the age of implantation on what their trajectory of verbal language adoption was. Now, if I had the less than 12 months, it would be very, very close, right here, to the normal hearing line.

So one of the things the CDaCI data tells us is that the earlier you implant, the better the performance on the median will be and closer to the adoption of the trajectory, and it's the learning trajectory of the normal hearing child.

The next phase that they looked at was speech recognition, which is what Dr. Eisenberg spoke about this morning. What I want to show about speech recognition --

again, you have a trajectory for your normal hearing child, and then there's trajectories that are plotted for the median for three implant groups: under 18 months, 18 to 36 months, and greater than 36 months. The thing I want us to realize when we talk about the time to follow-up, it's very easy in 3 to 6 months for a child, especially we're talking somebody under the age of 3, to identify what trajectory they're on, whether they are seeing a benefit from the therapy or not.

What I have here is showing you the graph for all 188 patients in the study. The solid line is the median line of performance. You've got the 25th percentile, the 75th, and the 95th percentile.

In terms of talking about what to do -- so we not only have to look at new technologies going forward, but both Cochlear, MED-EL, and Advanced Bionics, all three of us have existing technologies today that unfortunately are not put on a lot of children. We talked about off-label use today, but there are still healthcare providers who legally don't want to be held liable for off-label use. So, unfortunately, in those centers, they're still fitting with a sound processing strategy that's over a decade old.

So what we have plotted here, again from the population of 188 patients, is we have the cohort of the Advanced Bionics patients. The yellow line is the HiRes strategy -- again, it's over a decade old -- and the red line is the median for Fidelity 120 patients. So, again, what this shows, both of these sound processing strategies are well known, well used, and if we were just today to be able to fit children with Fidelity 120, you would see the increase in the median of performance. And for children from 0 to 3, it has a tremendous impact and benefit and what they could be missing out today.

So conclusions. I'd like to suggest that the CDaCI study does provide a viable alternative to not only a premarket but a postmarket study. The principal investigator for the CDaCI study is Dr. John Niparko. He would be more than happy to share this information publicly and also with the FDA so they could do their own analysis on the dataset. We have presented this before. There has been a huge amount of analysis looking at the other factors that limit CI benefit in terms of socioeconomic information predisposing factors.

What I would like to say is that for both current and new sound processing strategies, they should be expanded to include the pediatric population, as long as the safety of these strategies is already proven or can be proven in the adult population.

I thank you for your time, and I advocate that you strongly give your opinions to the Agency because your opinion is very valuable and helps promote change. Thank you.

DR. WOODSON: Thank you very much.

Is there anyone else in attendance that wants to address the Panel? If so, you'd be given 3 minutes.

(No response.)

DR. WOODSON: Seeing none, does anyone on the Panel have any questions for the Open Public Hearing speakers?

(No response.)

DR. WOODSON: If not, then it's time for us to begin our deliberations, and the Open Public Hearing will be closed. Now remember that the purpose of the Panel deliberations is for us to discuss among ourselves.

I want to remind the audience that although this is open to public observers, public attendees are not to participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves each time they speak.

I'd also like to say just a couple of words. There are a lot of issues that have come up in the discussion today, and we have a lot of thoughts about what could be changed about the way products are labeled now or the way things are marketed. But I want to focus the discussion on what the FDA is asking for advice on, and it's about how to conduct the studies for applications going forward. Now, they will be happy to hear our opinions about other things, but what we're charged with, I want to make sure that we focus on that.

So we can start out by asking if there are any questions anybody on the Panel has for the FDA staff at this time. Yes.

DR. TOMBLIN: I think I raised the question earlier about who initiates, like, particularly the preapproval process, and that was the manufacturers. But I think now we're talking about this sphere that has to do with, I guess, the kinds of expectations or standards that the FDA asks of the manufacturers, I guess, in this process, that is, can they use -- do they have to have pediatric populations in the sample and so forth? So that, I assume, is something that can be done by the FDA without the requirement of the manufacturers. That's sort of policy that is set by the FDA, not on the initiation of manufacturers; is that correct?

DR. WOODSON: Dr. Eydelman is going to address this.

DR. EYDELMAN: So we cannot change indication for use for a device without the

sponsor requesting the change. However, we're having this Panel meeting obviously to obtain input that can be publicly communicated to the sponsors, but it is ultimately then so that they are aware of our openness to receiving such a request. But, ultimately, until the sponsor comes in with a request to change the indication for use, we cannot do that.

DR. MADELL: If I understand correctly, we heard from several of the sponsors about the difficulty of what -- I understand, and that's perfectly reasonable, that the sponsor has to come to the FDA and say we need to change criteria or we want to change criteria. But we've heard from several of the sponsors today -- of the manufacturers today about how difficult it is to provide the data. So I mean, as a clinician, sort of the elephant in the room that we haven't discussed is that although it's not the FDA's problem, it is a fact of clinical life that if it doesn't meet the FDA criteria, the insurance company may choose not to support it, which means that the kids don't get implanted a lot of the times. And if we can't -- if we believe that early implantation, as an example, is important, I'm wondering if there are ways of getting around this.

DR. EYDELMAN: So let me try to clarify it one more time. The sponsor needs to come in to ask to change their indication for use, let's say to change the age that the device is approved for. What we require to allow such a change is what we're discussing today. Did that help delineate the differences?

DR. TOMBLIN: This is Bruce Tomblin.

And those decisions, essentially what it sounds like to me, the policy of the FDA as to the requirements that you ask of them, that can occur -- the manufacturers don't have to ask you necessarily to change those. It sounds, in fact, as though the FDA is entertaining

that, and that's what we're talking about.

DR. EYDELMAN: Exactly. That is exactly why we're having this meeting, to try to understand what is the absolute minimum requirements that we should be asking the manufacturers in order to allow for such changes once they ask us formally for them.

DR. WOODSON: But still, they have to ask.

DR. TOMBLIN: It sounds like there's a chicken and the egg kind of problem here and if somebody -- I guess maybe there has to be a willingness on one part, on the part of the FDA to be open to that. The manufacturers then have to understand that you might be receptive to their approach, and this is what this whole process is about.

DR. EYDELMAN: Yes.

DR. TOMBLIN: All right.

DR. WOODSON: Exactly. It's the responsibility of the manufacturer to get the proper approval for the product.

DR. HIRSCH: Barry Hirsch.

So aside from the age thing, whether that gets dropped from 12 to 9 months, we still have three manufacturers that have three fairly different criteria for thresholds. So one of the questions we're faced with is can we use postmarket data to make changes to the premarket indications? And I don't think we have that. What we have in adults is totally different, their criteria are different. So how do the manufacturers come to the FDA with -- well, it sounds like they would need PMA data to justify changing their implant criteria.

DR. EYDELMAN: So I think it will actually be clearer once we start going through the questions, but that's how we designed questions. We tried to sort of step through all the

different aspects of the applications that we would normally be asking, and we're trying to get your input on each aspect of that so that via this meeting we're being transparent to the manufacturers, who as you heard are all in the room, and the rest of the public. As you know, these meetings are public and then the transcript is publicly available as well. So your recommendations will become known to the industry.

DR. WOODSON: Yes, Susan.

DR. NORTON: If I understand what the FDA is asking us for, a postmarket -- a shift to postmarket studies, the manufacturers could take published peer review literature on age of implantation and the effects, which generally occur across manufacturers, and use those data or data from Europe, not just the United States, and say, based on the currently existing data in the literature, the peer-reviewed data, then we are asking you to move the criteria to 9 months or to a lesser degree of hearing loss. Is that correct? Am I interpreting what you're asking correctly?

DR. EYDELMAN: So what we're asking is what your recommendations are about this. Now, a Panel only makes a recommendation. Then we take all of your recommendations and we visit our internal opinion and then come up with a consensus about how we're going to move forward. So this meeting constitutes a very important part of our decisions about how to move forward, but it is not equivalent to the decision.

DR. ISHIYAMA: I think there is substantial data already reported, especially out of Europe, to implant children way younger than 12 months of age, and the outcome is superior. So I think the industry needs to perhaps then come up with a proposal based upon what's currently already available and present it for revised approval. And I think the

industry needs to do that because the data is already out there.

DR. MADELL: But I think it would help if the Committee also made that same recommendation.

DR. NANDKUMAR: I just wanted to circle back to what Dr. Hirsch was asking. Were you asking, because the manufacturer comes first with a PMA, because the criteria are so different right now for all of the devices, how do you make it uniform if they come -- I mean, was that your question? Okay. So I guess one thing that I might want to say is that there is CMS that's also asking the companies to do a study with the same indication across the board, and we have had discussions with the companies where we have tried to see if they could leverage those clinical data to see if they could make -- I think they are all interested in making those criteria uniform, and so there is some synergy there between those studies and what we would need in our PMA application. So there is some effort going on in that manner, even though they have to come first to us, but they are aware of that.

DR. HIRSCH: Barry Hirsch again.

Would that require another PMA in order to change the criteria? From each company.

DR. NANDKUMAR: Right. A PMA supplement.

DR. HIRSCH: So that's just what Dr. Norton said. If you look at all the data that's out there published -- European -- MED-EL could go to Advanced Bionics and say give us your data, and make that eligible data, I presume, to unify the playing field. Can they go to data from other companies?

DR. NANDKUMAR: They will have to make -- I mean, it's like they will have to make a case that those are poolable data. I mean, it's not the device similarities and designs and what it is. That's a little bit more of a complicated question statistically and clinically and design-wise, is that data poolable between devices like that, between -- what they could do is their own device. If there is data out there and various other forms of data that we were asking questions about, you could get postmarket based on peer-reviewed studies and stuff like that.

DR. EYDELMAN: So let me just clarify that the data is confidential. Only aspects of the data that are released at a public hearing like this or in the labeling or in SSAE, Summary of Safety and Effectiveness, is public. But there are lots of other data that gets submitted to us that is considered confidential. So we cannot utilize data of one company for approval of another.

DR. HIRSCH: Barry Hirsch.

But what if that data is published from that other company? In other words, if it's out there in the published literature, can Company A look at Company B's published reports and say we want to incorporate that into our criteria? Is that a legit avenue?

DR. EYDELMAN: Again, this is a PMA, it's a Class III device, so each dataset has to support reasonable safety -- a reasonable standard of safety and effectiveness. The company theoretically could try to make a case, but they would have to address the differences in design, differences in device, differences in clinical trial, differences in the population studied, et cetera, and also have access to the data of the competitor, which is usually not the case.

DR. NORTON: I think Dr. Hirsch misunderstood what I was saying. I was saying there are published data like the Niparko study, Niparko and Eisenberg and colleagues, that was all done in a standard method, but they had patients with each type of device, so each company could use the data from that published study, separating out, like Advanced Bionics did, the people who had their device. I wasn't suggesting that we could pool data across devices. I mean, there may be papers out there -- I'm not aware of them in pediatrics -- if you do exactly the same thing and have the same entry criteria that showed the advantage of one over the other. But I'm proposing that the companies be allowed to use -- to submit, for a postmarket amendment to the criteria, published data on their device.

DR. EYDELMAN: So the company is always allowed to submit any data that they choose to, to ask for anything that they want.

DR. NORTON: Okay.

DR. EYDELMAN: They don't need special permission. The question is can they make an adequate case that will warrant an approval?

DR. NORTON: So without doing their own -- I guess we're discussing -- I'm getting really confused with the time shift. We're discussing whether to allow the application of cochlear implants if the candidacy criteria can be expanded without a premarket study, but with a postmarket study. Is that the question?

DR. WOODSON: As Chair -- Dr. Woodson -- I'd like to kind of clarify. And FDA staff, if I misspeak anything, let me know.

I think we have to really keep clear in our minds the differences between what the

FDA is authorized and set up to do, what insurance companies' prerogatives are, and what physicians' knowledge and judgment tells them. And we have this issue where the physician can sit and look at all of the data and make a decision of what he thinks is best. The FDA has to look at what's submitted to them from the companies, and they're constrained to make the decisions based on that, along with their criteria. The insurance companies, on the other hand, there's a lot of variation between all the payers in terms of who they listen to when they make decisions.

So it's not possible that our Panel sitting here is going to come up with the entire solution to the problem. What we're trying to do is -- what the FDA has asked us to help them with is to say if they can expand the criteria because it's not so feasible to do these studies in small children. So how much can they borrow and transfer data from other things, either from other populations or to do studies? Let's go ahead and do these implants in a controlled way and follow them. Is that an adequate summary?

DR. EYDELMAN: Perfect.

DR. WOODSON: Okay, Sujana.

DR. CHANDRASEKHAR: Sujana Chandrasekhar.

So a couple of points that I wanted to bring up. I had mentioned before the concept FDA presented, that prelingual was age 6 and above, and I think that we've seen very clearly that there are younger children with pre- and postlingual deafness and older children with pre- and postlingual deafness. So I think that using an arbitrary age cutoff to distinguish pre- and postlingual is not valid and will invalidate interpretation of adult studies for children if we're looking at different causalities of hearing loss and time of hearing loss.

I think the other point that we need to make -- one of the industry presenters talked about 1 year out, 2 years out, but we're seeing with small children, particularly prelingually deaf children, that we may not achieve the hearing benefits that we want to see until 4 or 6 years out. So my interpretation of that is I think it makes quite a bit of sense to use the adult data to enable children to take advantage of what seem to be better processing strategies, better programming strategies, younger. But then the postmarket studies need to be extended out for a good 5 or 6 years so that we can really capture the benefit over a predictable lifespan of time to achieve the hearing and educational outcomes that we would like to see from the implants.

And then the third point is we've mentioned data registries, and I think it's very clean when that data comes not perhaps from the manufacturers but from the clinicians. And I think then you capture the children who move from one state to another if you have a national data registry. Let's say the American Academy of Otolaryngology is setting up data registries. So if we have that data registry that's national, then the child can move wherever they want, and their outcomes can be tracked appropriately within that registry, and that will give us a better snapshot of what actually happens to these children than trying to do an implant-specific registry or a center-specific registry.

DR. WOODSON: Thank you.

Yes, Marly.

DR. KENNA: Marly Kenna.

I have a question about -- it seems very much from so many of the presentations that there is existing data, especially if we looked hard enough perhaps, to answer some of

the questions with the existing adult data, but there's obviously also data that doesn't exist.

My question is, once there is a list of questions that we want to answer, who is responsible for figuring out where the holes are? And then who is responsible for helping us figure out what the next steps are? Just to take, for example, single-sided deafness. I think there are very little data in the adult literature and none in the pediatric literature, but it's clearly something we'd really like to know about.

So the question is, who looks at the available data? And then who says we have enough or we don't have enough and then actually may go out, like the NIH occasionally does, and have an RFA and say we really need data for this? And then what's the mechanism of that? Because I think a lot of the things we're talking about, there isn't enough data, but we sure wish there was, and how to identify that and then how to get that data is, to me, not a clear-cut pathway.

DR. EYDELMAN: So we hope that today's discussion will help us delineate where the holes are. That's what we hope to walk away with at the end of the day. And also we hope that this public forum will highlight the need to generate data. And you, as the leaders in your field, will reach out to your other colleagues via NIH or an academy or any other professional association and help us help the industry obtain that data.

DR. WOODSON: Yes, go ahead.

DR. TOMBLIN: I think an example that was just raised is, is there a mechanism or a means by which the FDA can approach the NIH to say this is an area of considerable need on our part? Can you create an RFA in this area? I know, obviously, the institute then has to decide, among all of its different priorities, where this comes. But I would think it must

have been going through a lot of our minds that, oh, yeah, we as individuals can try to do this, but the FDA probably can speak with greater authority and greater strength to NIH than any of us.

DR. EYDELMAN: So we do have many collaborations across different government agencies as well as with many professional organizations, as you heard from this morning's presentations. I believe the clearer the message at the end of today, the better the ability for all of us to take next steps.

DR. SCOTT: I think we heard from one of the presenters -- I think it was Dr. Hughes -- around kind of within even the younger population -- I think under 6 -- there's even a subpopulation within that that has better outcomes or they're more clear for the use of these implants. So the question is, does the FDA have the ability, I guess, to have subsets even within specific age groups or recommendations for within a subpopulation?

DR. EYDELMAN: So I will leave it to Shu-Chen, but as she said, we're looking for your recommendations of how to group the ages, specifically for pediatric cochlear indications, because we're not necessarily following the exact definitions per FDA guidance of what the pediatric versus adult is. As Shu pointed out, it's greater than 21 that's considered adult, yet we're looking at 18. So, once again, we hope to get very specific recommendations about each of the age buckets during your deliberations.

DR. PENG: Right. I also mentioned in the presentation that, aside from the chronological age, there are other patient factors, including this one, you know, for the onset of deafness, pre- versus postlingually deaf. All of those can be considered, not just the chronological age, and we don't necessarily have to have like -- it really depends on the

proposed change or, you know, modification itself, too. So we're here to listen.

DR. WOODSON: Do you have any thoughts about how industry, as a whole, might be thinking about these sorts of recommendations?

DR. VON JAKO: Yes, thank you. Yes. Ron von Jako. So thank you.

I think, with the industry, that the -- you know, looking at the trial design and how to set it up and the limitations and extrapolating the data that I heard this morning, from adult to pediatric, what a meaningful study design would look like and how you would choose the populations and be able to set up a protocol and follow them, et cetera, could be extremely difficult and may not be consistent.

And as I was listening to all of the speakers and the discussions here, I was also thinking that -- and this is just putting it out there -- if the three manufacturers got together and came up with some criteria on how they would segment studying children 6 years younger or 6 years older and what the concerns are on how to extrapolate data and so forth, and came up with kind of a criteria document that they could present to the FDA and agree on it among themselves and look at how they would then choose on when they would set up a study that would be postmarket versus premarket data, when literature would be combined with maybe a smaller study or just when the literature itself would be enough, or when if there are design changes that impose any safety and risk or efficacy concerns, then they would go for a complete study, and just some kind of an agreement among themselves that they could present to the FDA, that there could be some kind of a guidance document to follow.

DR. WOODSON: Is that something that could be helpful to the FDA?

DR. EYDELMAN: Definitely. And it has been done in many other areas.

DR. WOODSON: Okay. Actually, Ms. Broyles had a comment.

MS. BROYLES: I just wanted -- Susan Broyles, sorry -- to comment on a couple of things. First of all, I agree with all that he just said. And also, as far as the adult criteria transferring to pediatric, after being my mother-in-law's major caregiver throughout her -- the process before she got the implant, much of what she experienced is very similar to children who have never heard, because she had gone over 10 years with profound -- I mean, she couldn't hear anything. And she, just as her mother and sister -- but they died earlier. But my mother-in-law had no other health issues at all. So once we got her hooked up with that, it really was like a switch being turned on. It was amazing that she could lead over to that. I mean, she had to relearn many things, you know, because their whole life -- everything changes. And, of course, she at first said, I don't think this is loud enough, you know, and this isn't going to work, but it was just truly amazing.

And the same criteria that they measured through the center in Dallas was much like what you all had discussed today, because she truly was like -- the fact of not being able to hear really impacted everything she did besides mentally, you know. And she's very outgoing, so it was very difficult, but it was like turning her back into an adult. It really was very similar.

And I've been impressed with all of the speakers because it's a very exciting thing just to think that children, who already are innocent and there's nothing that they have to judge prior, just a miracle of them being able to do that is amazing.

DR. WOODSON: Thank you.

Dr. Nelson.

DR. NELSON: So the breadth of some of these questions overwhelms me a bit. So I was looking at Question 1 and the different parts of that, what we've been asked to do, and still, that's a lot right there. But I was thinking about the data that we have seen today and that others exist about some of the expanding of the criteria. I mean, that seems to be that those data are going to be about prelingual children, especially if we're talking about less than 12 months of age, right? Or perhaps asymmetries, as Dr. Gifford showed. That's one category of the children that we're thinking about. There aren't really any adult data that we can extrapolate to that scenario, but we have quite a bit of data on the efficacy of expanding those criteria. So that would seem to be one thing that I'm drawing from today's discussion.

Another is that there are some of the device modifications, that it seems like, well, duh, waterproof them without having to ask for multiple studies and that we don't need to even worry about extrapolating adult data because that would seem to lead to fewer device failures than not water. But some of them seem to fall in the middle to me. Like, is beamforming going to work for children as well? Is it going to work -- is automatic scene selection going to work as well for prelingually deafened children versus post-ling? So there are few that fall into different categories, to me. Are we going to kind of break those down? That wasn't really a very good --

DR. WOODSON: No, no, no. It really was, because I was sitting here and looking -- you know, we have all of this time to sit here and deliberate, and then we have this time to look at the questions. But it might be better, I think, at this point, to really start focusing on

the questions, because that's where we want to get the detail. So if we really want to -- I think now that we kind of have it in our heads what it is we're supposed to be doing, maybe we should do this. So this is a good idea, and maybe we'll work some on the Panel questions, a couple of them, and then take a break, because there's four questions, but each one has a lot of detail. So yeah, let's start focusing on Question 1.

DR. NANDKUMAR: Dr. Woodson?

DR. WOODSON: Yes?

DR. NANDKUMAR: We can project the questions.

DR. WOODSON: Okay, that would be great. Yeah, the first question, I'll read it before it flashes up.

Advances in cochlear implant technologies and certain changes to the indications for use may be suitable for a shift in some clinical data requirements from premarket to postmarket data in pediatric patients, especially in patients younger than 6 years of age. Clinical data could also be leveraged from adult populations and children older than 6 years of age to support this "premarket to postmarket shift" in clinical data requirement. Please discuss and make recommendations regarding the clinical data requirements to support premarket approvals for the following changes to cochlear implant devices in pediatric patients.

So there's a list of these and then there is, down in (c), is there anything else? We've heard from one of the guest speakers of the dangers of maybe making this a closed set and that we might want to make sure we leave some room. Let's see how we can work this because Part (a) has to do with the coding strategies and then there's the other

modifications. But let's start talking about the coding strategies.

You have started out by giving us some thoughts, Dr. Madell. Why don't you tell us what you think about --

DR. MADELL: Okay. Susan Norton brought up something earlier which is certainly an issue. There's no question that a child or an adult could end up having a surgeon who is doing their first cochlear implant on them, and an audiologist who has never met the child. There's no question that that can happen. But I think we should assume that we're dealing with professionals who have ethical concerns, and we should assume that the professionals are doing what is appropriate. Are there going to be people who don't? Yes. But that's not the responsibility -- I mean, if that were the criteria, we couldn't do cochlear implants at all. I mean, we wouldn't be able to allow cochlear implants if we had to worry about whether everybody was going to do them appropriately. So I think we should assume that people are going to do this appropriately.

By that I also mean that we have to assume that an audiologist will make an appropriate decision based on the child sitting in front of them. Most audiologists, when we're fitting hearing aids, we don't turn directionality on usually until the child is consistently knowing to look at the person who is talking. Otherwise you end up with the child hearing, you know, not knowing where to look and not getting good information. The same with beamforming. We don't have to turn everything on just because it's available.

DR. WOODSON: So you're saying that these speech-coding strategies are something that wouldn't have to be turned on all the time and you turn it on --

DR. MADELL: You could choose the appropriate speech-coding strategy depending

on --

UNIDENTIFIED SPEAKER: But (b), (b), not (a).

UNIDENTIFIED SPEAKER: Front-end processing.

DR. MADELL: Yes, I'm talking about front-end processing. I'm talking about, in general, we have to assume that there's a professional involved who is going to be making decisions, and we don't have to decide, for each one thing, whether it can be moved. That's all I'm saying.

DR. WOODSON: Okay. Marly, do you have any additional comments, other than what you said? Okay, Marly.

DR. KENNA: I think you bring up a good point. I think that it's reasonable with somebody who is well versed in the strategies. I don't know currently if -- I know that all audiologists who work with cochlear implants are probably not cochlear implant certified, and we really haven't talked about training here or certification or anything like that. But I do wonder, as this gets more complicated, whether the people who are doing the mapping and the coding and the interpretation actually will need to have some basic level of training. That would be my only question.

DR. WOODSON: Okay. So, David, you and I are both head and neck surgeons, but based on what you heard today, what's your thought?

DR. TERRIS: Well, so -- yeah. And I think there's some benefit actually to not being a neurotologist or an audiologist, so we have a little perspective. But I would say again, as I sort of suggested earlier, it seems like reducing the burden on the cochlear implant manufacturers, in net, is going to benefit society. So we want to maintain safety, but we've

heard very little in the way of concerns about safety. So I would say again, I would support, on this specific point, using postmarket data to allow them -- and again, we're not going to legislate exactly what they need to come with, but giving guidance to the FDA, I would say it makes sense to use postmarket data, adult data. It seems in most circumstances to be appropriate to apply it to the pediatric population.

DR. NORTON: Referring to Question 1a, I think that speech-coding strategies can be moved from a premarket to a postmarket shift and that adult data and data from older children can be extrapolated to pediatric populations in terms of the clarity of the information, the richness of the information being provided.

DR. ISHIYAMA: Yes, I agree.

DR. WOODSON: Scott.

DR. BRIETZKE: I also agree. The risks are low and the benefits high.

DR. WOODSON: Okay. Dr. Tomblin.

DR. TOMBLIN: I also agree, with regard to (a), with Susan. It seems to me the data are already there that show that we've got a variety of speech processing strategies that have come along and things are pretty stable with regard to those results both in adults and children. So I think in regard to using adult data to extrapolate to children, with regard to speech processing strategies, it seems justifiable. And certainly if there's some question, then postmarket data would always be good to further confirm that.

DR. WOODSON: Dr. Houston.

DR. HOUSTON: I would agree that the chances that any change in speech-coding strategy that would benefit adults or older children, that it could possibly be a detriment to

younger children is very, very, very low.

DR. CHANDRASEKHAR: Sujana Chandrasekhar.

I also agree that the shift from premarket to postmarket clinical data requirements for speech-coding strategies is worthwhile. I would also just remind or just reiterate that when we look at postmarket in children, we should look for longer than a year or two. We should look for enough time so that we can actually see if there are benefits or detriments.

DR. WOODSON: Dr. Hirsch.

DR. HIRSCH: Barry Hirsch.

So it will remain to be seen whether they do exhibit benefit or efficacy from using these speech-coding strategies. The representative from Advanced Bionics specifically spelled out my concern. Is there a risk or is there a safety issue regarding impulse charges that would go to the device using these coding strategies? And at least one company said there should be no risk. So since there's no risk and there's only the upside, I'm in support of that same concept.

DR. WOODSON: Okay. So, Dr. Eydelman, it seems everyone has concurred, as far as Question 1a, that we would agree.

DR. EYDELMAN: Thank you.

DR. WOODSON: Now, I think 2b actually has two main components. Oh, yes?

UNIDENTIFIED SPEAKER: 1b.

DR. WOODSON: 1b. I'm sorry, I'm really jumping ahead.

(Laughter.)

DR. WOODSON: I'm thinking about everybody else's plane.

Okay, 1b. It has two main components that we could -- there's device modifications and changes for indications in use. So maybe let's look at device modifications. And I might just ask right now, is there any one of these three device modifications that someone would want to maybe take off the consent calendar and say needs to be discussed, or is there some concern from anybody that any of these should not have the data moved to postmarket testing? I think we're all in agreement that the waterproofing is not an issue.

DR. WOODSON: Okay. Sujana.

DR. CHANDRASEKHAR: Sujana Chandrasekhar.

I think there has been a great deal of concern by the clinical audiologists regarding the front-end processing, and I think that's something that we need to just be a little bit more clear about. But the others, no.

DR. WOODSON: Why don't you expand on that, and then we'll get other people's thoughts on it.

DR. CHANDRASEKHAR: So what I'm hearing and my experience is that the same type of noise reduction or beamforming, making the sound be from a particular place, that we use for adults to be able to concentrate on hearing in noise may not be appropriate for children because, as we've heard, children hear by overhearing. Children really do take 360 of sound in so that they can figure out their cadence, the importance of different things that they're hearing. There's so much more to hearing than just taking an acoustic stimulus and processing it in your brain.

So I think that the sub No. 1 really has to be spelled out that this -- any of these changes have to be done in the context of knowledgeable programming strategies by a

trained audiologist who either has experience with young children with cochlear implantation or can access that experience. And that's where one of the slides from FDA this morning was about the teleconferencing or the telemedicine, where you have a more experienced audiologist some place and you have the audiologist in front of the patient in another place, and that's something where you can really use telemedicine to make sure that every bell and whistle is not being turned on just because they exist.

DR. WOODSON: So the front-end processing is something that can be turned on or turned off.

Susan, do you have some comments to make on this?

DR. NORTON: Yes. Well, everything that Sujana said and I think what -- in relation to Question 2b, I guess the FDA is asking if these can be moved to postmarket. The problem is the same -- and again on the programming software. So what the companies have done with their software, even, they have general software, and they've set many of these preprocessing strategies as the defaults.

When you do programming, we have data that -- I don't know that we've done systematic -- anybody has done a systematic study, but certainly clinically, children end up with inappropriate strategies for preprocessing for the task of learning language and acquiring information. The problem is that the preloading of these strategies assumes that the listener actively can change the program for the listening environment. A small child cannot, most children do not, and most parents do not. And it's only by them coming in and not making progress that we say, oh, gee, no wonder you never respond. You're on this tight beamforming or zoom. So I don't know how the FDA addresses not having these

strategies be -- these preprocessing strategies be default programming options in the software. Is that a legitimate concern?

DR. NANDKUMAR: Yes, that's an excellent concern, and we have the same concern, and we have conveyed that. My impression was that they were not default.

DR. NORTON: They are default.

DR. NANDKUMAR: Okay. So we will make sure that we continue those in that same way. So we completely agree that they should not be default settings.

DR. NORTON: So that -- yeah.

DR. NANDKUMAR: Yeah.

DR. NORTON: So if you extrapolate, you cannot extrapolate from adults to small children in these instances.

DR. NANDKUMAR: Right. So it will have to be the decision, like you said, of the programming audiologist who makes that decision based on what the child can -- the way the child is responding.

DR. NORTON: Yes, the age and all that.

DR. NANDKUMAR: So I just wanted to make a clarification while this discussion is going on, a clarifying question for the Panel to consider. One of the reasons why FDA, traditionally or historically, has been concerned about the application of these new speech-coding strategies and new front-end processing strategies to be turned on either as default or turned on in children as the next new thing that's coming down the road kind of thing by an audiologist or a programmer, it was because we have seen data in adults, especially for the speech-coding strategies, the newer speech-coding strategies or the newer front-end

processing, that some others do good and some don't. Some have a preference, some don't.

So the distinction point. Like Dr. Chandrasekhar made, if it's the prelingual deafness versus the postlingual, the postlingually deaf person can give that feedback, that I don't like this, turn this off, after using it even for probably like a few weeks or a month, something like that. So the concern we had had was for the prelingually deafened children, for these new things that come down, is whether -- they don't have that choice. So if their audiologist turns it on, they have it on. And is that something you -- as experts in this area, are you concerned that that's the critical learning period for that prelingually deaf child, in those early ages of 1 through 4 or whatever, through 4 or 6 or whatever it is? Are you concerned about that? If we do this postmarket shift like you recommended, is there any concern?

DR. WOODSON: Dr. Houston, you had a comment?

DR. HOUSTON: Yes. Actually, I kind of have the same question. Well, what I'm hearing from the audiologists in the room sounds like, to me, is that there might be reason to believe that the auditory needs, you know, vis-à-vis these front-end processing strategies, noise reduction and things like that, might be different for young children than they are for older children and adults. And if that is correct, then it seems to me then we would not want to allow data from adults and older children to speak to modifications for younger children.

DR. MADELL: I want to answer Derek. I think it's not that it's never appropriate. It's that sometimes it's appropriate and sometimes it isn't, and a clinical decision has to be

made about how to use it. In my view, it should be allowed, and an experienced pediatric audiologist should make the decision about when to turn it on. I mean, this is the same thing as all the original studies on rate. The manufacturers set as the default the rate that was the most popular. But the truth of the matter is, almost an equal number of people had a different rate that was better for them.

So in work with adults and with children, the audiologist needs to look at the data, needs to look at the progress the person is making, needs to see whether the child is making 1 month's progress in 1 month's time, and if not, say we need to change something. But it's not that this shouldn't be available for children. It should be. And a skilled professional should make the decision about how to use it.

DR. KENNA: Marly Kenna.

I think that's what I was trying to get at when I made my comment about training, is that I think -- yes, I think it would be great to have this available. There are going to be some children who will benefit from some of these strategies in some situations, especially the ones with really good language. And some of them have great language. But you have to know which strategy to use and which child. And I think, as Dr. Norton said, sometimes you see a child and they're doing very poorly and their strategy has been implemented by someone else who really didn't get the child and the child is making no progress. Now, how to deal with that and assure that there is an experienced audiologist, I don't know the answer to that, and I don't even know if that's within the purview of the FDA, but I don't think it's enough reason to not make these strategies available.

DR. CHANDRASEKHAR: Sujana Chandrasekhar.

So I'm hearing that the inherent potential harm to the child of the wrong front-end processing is that they don't move forward month to month. So if you let them go a year, you've lost 12 months. That's a little crazy. But if you see them in a month or you see them at 2 months and they're really not going where they need to be going, I have to say even the worst audiologist knows that something has to change. And really, I mean, we need to protect our patients from the worst physician and the worst audiologist combination and the farthest distance to healthcare combination, right?

So if the education happens to the physician, to the audiologist, and to the patient/parent, that they should be expecting improvements at every visit. And if they are not, then one of those three characters has to intervene and say something is wrong. Then I think we are providing that safety net so that when we apply these adult technologies to children, we're not just applying them and leaving, but we're applying and following up.

DR. WOODSON: So -- oh, yeah, Dr. Hirsch.

DR. HIRSCH: What I think I hear you saying is that the concern would be in the prelingual child who you've got to take one of these coding strategies and you don't know what's the right one. You know, have you made a wrong decision about a prelingual child, and how can you monitor their progression or not? I think what Derek said earlier is that, you know, these kids are super plastic. So this is like hey, listen, we're going to either teach you how to speak Chinese or French. There are two different languages, but you're going to learn one of them, and perhaps with these coding strategies they will be able to adopt that and they will say this is how I'm supposed to hear. If there's not progression, just like Sujana is saying, then they have got to change strategies.

DR. WOODSON: Susan.

DR. NORTON: So I think, like Derek said, with basic input in the speech-coding strategy and rate, young children are incredibly plastic, and they acquire speech, they learn a code, a language, with minimal information if they have rich exposure. The preprocessing is different because it restricts their access -- it can restrict their access.

So if I programmed someone 15 years ago with the then default rate of 1800 Hz or 900 Hz per channel, and then they get a processor where they have to switch to 500 Hz in order to have enough power, then that kid is really upset because I've changed his hearing. But if I started him out on a 500 Hz rate, he would be fine. That's his hearing. But then if you're starting to introduce these preprocessing strategies that restrict what he has access to and changes the loudness of the speech up and down at will, I mean, you're doing something entirely different. So I'm not concerned about the speech-coding strategy. I'm concerned about all of these preprocessing strategies being introduced.

DR. WOODSON: Dr. Houston.

DR. HOUSTON: Derek Houston.

Yeah, I just want to reiterate what Dr. Norton said. I see these as two very different things, the coding strategies versus the front-end strategies. And I guess I also have a question because if the manufacturers are required to have premarket approval to market a particular front-end strategy for young children, does that necessarily mean that the clinicians cannot use that strategy, that front-end strategy? Right? I mean, they still can, right? This is more about what the FDA wants to put its stamp of approval on, that the FDA feels that there is sufficient evidence out there showing that these particular front-end

strategies are beneficial or at least not detrimental to the efficacy of development in each of the age groups that the labeling is for, right? And I guess I'm just wondering if we have enough data on that.

And I guess the question then comes down to whether we think that the adult and child data are applicable to the young child data. And I'm not an audiologist, but I guess what I was hearing from the audiologists is that there's reason to think that what the children -- what young children need as far as front-end audiological information might be different than what older children and adults need.

DR. TOMBLIN: Well, I think actually you were on the same track as I am. Presumably, the devices that we're talking about here could come with the potential for beamforming or not. And now the question is -- and it's been demonstrated in adults to be efficacious and so forth, so that it's built into the device, but it's an option that you can either have it on or off or noise suppression on or off and so forth. And so therefore the issue would be whether the FDA would say, in this subpopulation, we would recommend or -- I guess that's all you really do. Things can always be done off label, but on label, this device would be used by having it configured in this way.

And so it would seem to me as though you wouldn't be able to take adult data and extrapolate to children with regard to the issues we're talking about here, because we're talking about them as we believe they might impact language learning, and that's not going to be answerable with adults. It seems to me as though -- now, it's always -- since it is the case that the option is there, it would always be available to the audiologist to do. Now, I guess, at that point they would be going off label.

DR. WOODSON: So the consensus I'm hearing, and tell me if I'm wrong, is that as long as this is set as a default to have it turned off and people would have the option to turn it on, then it would be fine to give a premarket -- have any real testing of this done in the postmarket setting. Anyone disagree with that?

DR. ISHIYAMA: And the other thing is, can we add to say this should be done by experienced pediatric audiologists? I think that's critical because --

DR. WOODSON: I don't think there's labeling for that; that's the problem. Yeah, that's the problem. But I think if we say -- so the default setting would be to not have the front-end.

And the other thing that I'm getting is to turn on this beaming and stuff, you're supposed to turn it on when you're trying to focus on somebody, and if you're just, you know, a kid who was looking at everything, maybe it doesn't help you. That's my takeaway from this. So are we in agreement on 1b(i)? I feel like I'm doing bingo.

Dr. Eydelman, is that sufficient?

DR. EYDELMAN: Yes, thank you.

DR. WOODSON: Okay. Now we're getting to the programming and mapping software. Does anyone have any issues they want to bring up with that? Nobody can think of anything bad that could happen with that?

DR. KENNA: The same issues, yes.

DR. WOODSON: Oh, the same issues. Okay, tell me what the mapping does, because, like I said, I'm a head and neck surgeon. So I know that you kind of turn it on and you see if they hear better and the kids can't tell you if they hear better. What's the issue

here?

DR. CHANDRASEKHAR: So the dumbest person in the room is now going to explain one of the hardest things that we're talking about. Just like a hearing aid is programmed to enhance the frequencies that the individual is missing, the cochlear implant is programmed in a similar way, but with a much more degraded hearing signal to begin with and maybe with no hearing signal. So the programming is done when the person is able to cooperate by saying, oh, I really like the way mom sounds with this program, and I don't like it in that program. We don't have that ability with children, so again we use those threshold and comfort levels to figure out a median where the child will be hearing enough sound without it hurting them, and then as they progress, that program can be fine tuned.

DR. MADELL: Jane Madell.

And as we get information from the auditory therapist and the teacher of the deaf and the parent about what the child perceives and doesn't perceive, we can change the settings. So it's a group effort.

DR. HIRSCH: Barry Hirsch.

You know, this exists already. Kids get mapped with the existing software, and all you're doing is offering additional software that they'd have options to. So it's just extending the menu.

DR. WOODSON: So we don't want to make any special blocking on being able to use enhancements of mapping.

Dr. Eydelman, we seem to be okay with that one.

And waterproofing. This falls into --

(Laughter.)

DR. WOODSON: That falls in the "duh" bucket, I understand. Okay.

DR. NANDKUMAR: Excuse me.

DR. WOODSON: I think --

DR. NANDKUMAR: Dr. Woodson?

DR. WOODSON: Yes?

DR. NANDKUMAR: Does the Panel have any comments on remote programming, telehealth --

DR. WOODSON: Oh.

DR. NANDKUMAR: -- because that's part of this question, I think, enhancements to programming.

DR. WOODSON: Oh.

DR. NORTON: Telehealth.

DR. NANDKUMAR: That was one of the examples we gave in our presentation.

DR. WOODSON: Oh, in your -- okay.

All right, Dr. Hirsch.

DR. HIRSCH: First of all, it's not specifically spelled out for that request, you know, telemedicine. And telemedicine is a very tricky thing. You have to find how that kid is being programmed. Is it the person remotely who is actually setting the T's and C's, or is there an interfacing audiologist who's doing it? Is it just the technician who puts the device on the head and then the person remotely is turning your dials or whatever you do? But to set the T's and C's -- so you can potentially deliver too much sound or too much electrical

stimulation, and an audiologist would see that the child is reacting badly and turn it off quickly or take the device off quickly. So I do not have personal experience with programming by telemedicine, but that would be one of my concerns, is who are the interfaces on both sides?

DR. WOODSON: Let's go with it once. We'll go around this way.

DR. MADELL: Jane Madell.

I do have experience with doing this, and I do consulting in Jackson Hole, Wyoming, where there has been no -- there's no pediatric audiologist in the state of Wyoming, which is a little hard. So what we've done there is arranged with a cochlear -- a very experienced cochlear implant program in Denver to interface with the hospital clinic where there is an audiologist.

And so the child will come into the hospital where there's an audiologist and remotely work with the CI audiologist in Denver. So there's a human being who knows things in both places, and they're looking over TV monitors. So the audiologist in Denver is seeing the kid in Jackson Hole and talking to the audiologist in Jackson Hole, or sometimes it's the teacher of the deaf in Jackson Hole. But it's not like the audiologist in the CI center has the kid alone in a room and nobody is there. That would probably not work well. But this actually works very well. And so a family doesn't have to take 2 days or 3 days off to go to another city to get their kid mapped.

DR. KENNA: Marly Kenna.

We have experience because we have a fairly international patient population. So we have experience where we do map -- I don't -- our audiologists do map the children

trans-continent, and it requires training. Again, this is a training issue and experience issue, but it is entirely possible. We actually have a patient right now who's mapping herself. She's working at a program in Africa and has two implants, and she's using the remote mapping software to maintain her own map while she is in Africa. It's good software if used correctly, so I think it should be available.

DR. NORTON: So we're just looking at this issue and designing our own pilot program. But Dr. Hughes, who was one of our speakers this morning, has one of the most thorough studies on the issue of telemedicine and cochlear implant mapping. Are we allowed to ask her to make comments?

DR. NANDKUMAR: Yes.

DR. NORTON: Dr. Hughes, are you willing to talk about this?

DR. HUGHES: Unfortunately, I stepped out for a moment when you started this conversation, so I did miss the beginning of it. But yeah, the current R1 that I have is looking at specifically using telemedicine for pediatric mapping as one of the aims. And so we're focusing on the two main behavioral methods, so one group, a younger group, using VRA methods and then another group, the older group, using conditioned play audiometry. So did you have questions that were specific?

DR. MADELL: Does it work?

DR. HUGHES: Does it work? Well, it seems that way, but I'm not going to commit to an answer yet because we're just starting year 2.

DR. WOODSON: You haven't seen any damage from it, I take it.

DR. HUGHES: No, no. And at this point we're not doing full-blown mapping. It's just

comparing map levels that are obtained in a face-to-face condition versus remotely. And so our study is set up to where the expert clinician, the CI audiologist, is the one who's pushing the buttons, and then the person who is with the child in the remote condition is somebody who's less experienced. So it's set up so that ideally it would be, you know, the deaf educator or the SLP or the local audiologist, somebody that the child is familiar with, who is going to be there serving as sort of like a play partner. And the play partner and then the expert clinician are working together with each other to say things like yes, that was a reliable response, or no, that was a false positive.

DR. ISHIYAMA: Yes, I think MED-EL has quite a bit of data on this from Austria, and I think it's been also done in Russia. So I think this is something probably good to look at, and I think we should have it made available.

DR. HUGHES: The Vlastarakos study, is that the one you're talking about? Yeah.

DR. WOODSON: Dr. Tomblin.

DR. TOMBLIN: It seems to me the scenario we're mainly talking about here is where there is a clinician of some sort, an audiologist, maybe a speech-language pathologist, who is in the room with the child, and the telemedicine then is providing the expertise, which it seems to me now that kind of gets into the topic that's come up several times about, well, do we mandate certain levels of expertise for mapping and so forth? And we've said that that's off the table. We're concerned with the device and so forth. And it sounds to me like that's probably okay. It seems different from the African example where the patient is actually the only one there. And having spent time with grandsons on Skype, I can say it doesn't always work very well. They just don't seem to understand. They engage a whole

lot differently directly on Skype than they do face to face, but I don't think we're talking about that. I'm assuming that there would always be an adult with some level of qualifications that are engaging.

DR. KENNA: Just to clarify, for all of our patients that we're mapping remotely, the expert person is at our center and there is a child with another adult in another place, with the single exception of this young adult who has been implanted for 20 years and is mapping herself as she's in the Peace Corps.

DR. WOODSON: Dr. Hirsch.

DR. HIRSCH: Just a technical question of how you do it, Jane. Is it the person who's at the center who initiates the current that goes to the kid's implant, or does that person who's at the center and sends it to the remote site tell that person, okay, turn on this thing?

DR. MADELL: Jane Madell.

The person who determines the current is the expert in the CI center.

DR. HIRSCH: And they hit the button?

DR. MADELL: They hit the button.

DR. HIRSCH: So just like Skype, what happens when you lose your Internet strong connection?

DR. MADELL: You turn it back on again and you wait.

DR. HIRSCH: But what if you stimulate the thing and you have not the ability to turn it off? And somebody has got to know that the kid's upset.

DR. MADELL: If the kid's upset, the kid will -- if it's upset, the kid will pull it off.

DR. HIRSCH: And that little kid?

DR. MADELL: Oh, yes. I mean, a kid who can -- I mean, the kid will just go -- I mean, the tiniest kids go like this when they don't want it on their heads.

DR. CHANDRASEKHAR: So can I just ask you another? What is the exact question you're asking us, number (iv), which is written in invisible ink over there? So is the exact question, does the Panel feel like there's a role for telehealth in this?

DR. NANDKUMAR: No, no, it's the same as can the data for the children -- based on adult data, can that be approved for children?

DR. WOODSON: And then used postmarket.

DR. NANDKUMAR: Uh-huh.

DR. WOODSON: And then you look at it postmarket.

DR. NANDKUMAR: Yeah.

DR. HIRSCH: I would think it's more of --

DR. NANDKUMAR: It's the same question that we started with for all the subparts.

DR. HIRSCH: I would think it's more of subset (ii). You know, can enhancements to programming and mapping software -- that's an enhancement.

DR. WOODSON: That's the telehealth.

DR. HIRSCH: That's the telehealth that's in there, as opposed to that postmarket to premarket.

(Off microphone comment.)

DR. HIRSCH: Yeah.

DR. WOODSON: So as Chair, I call the question. Do we think it's okay to do postmarket studies on telemapping?

UNIDENTIFIED SPEAKER: Yes.

DR. MADELL: Yes.

DR. WOODSON: Okay. And we're not going to vote on the waterproofing because of the snow and all of that. Okay.

DR. NORTON: So wait a minute, I didn't vote.

DR. WOODSON: Oh.

DR. NORTON: You're moving way too fast for me.

DR. WOODSON: Really?

DR. NORTON: Yeah. So are we saying is it okay, without doing a premarket study in children, to program children remotely based on the success of adult data?

DR. WOODSON: Actually, it's already being done in studies and there's no way -- we can't tell somebody not with their judgment to do that. But the question is can the FDA say we are going to approve it, pending postmarket studies?

DR. NORTON: Okay, okay. Okay, I'll --

DR. WOODSON: All right. Does anybody else want to not vote for it? Okay, I'm sorry, I want people to get to their point, but I want to make sure I we have adequate discussion. So I'm glad you --

DR. NORTON: I don't have a plane until tomorrow.

DR. WOODSON: Okay, I see.

(Laughter.)

DR. WOODSON: All right, conflict of interest. I want to raise the hands of everybody. All right.

So now we're going to look at the changes in use, in indications for use. And it did seem like there was a lot of discussion going on around these issues, so we probably should take these one by one. Who wants to lead off discussion on the severity of sensorineural hearing loss?

Go ahead.

DR. MADELL: I feel like I'm talking too much, which is a problem I have.

(Off microphone comment.)

DR. MADELL: I know, that's why I said it's not a new problem. I just feel like I should be polite.

(Off microphone comment.)

DR. MADELL: Sujana is my friend, can you just imagine? Okay.

DR. WOODSON: Who are your enemies?

DR. MADELL: I have been a pediatric audiologist for -- I'm embarrassed to say that it's 50 years, and I've seen enormous changes. Severity of hearing loss is something we really need to change. It is no longer profound. That is the criteria that should be the criteria for cochlear implants. The question is, is the child hearing well enough with hearing aids? And kids with severe hearing loss may hear well enough in a quiet situation inside a test booth, but in real life they don't hear well enough. And kids with severe hearing loss, certainly 80 and worse, should be candidates for cochlear implants without having to go through hoops, and that includes young children, in my opinion.

DR. WOODSON: So are you recommending a certain level like 80 or worse, or are you saying that we shouldn't look at the hearing loss and we should look at whether or not

they do well with hearing aids? What would be something you would recommend? Put something up there we can shoot at.

DR. MADELL: Okay, okay. So for discussion purposes, let's say a pure-tone average of 80 dB -- I don't know if I want to say that -- I mean, certainly 80 dB or worse. But you could have a kid who is hearing at 70, 75 through 1,000 and then goes down to 110. So that kid has got some okay thresholds, but that kid is not hearing well enough to use hearing to learn. And so any -- I don't know.

DR. WOODSON: Well, let's let some other people comment and then you can clarify maybe.

DR. MADELL: Okay. So I mean, I think that we need to open it up to severe hearing loss. Let me say that to start with.

DR. WOODSON: Dr. Kenna.

DR. KENNA: So I agree. I think that we should open up to children who have more hearing, and I think, off label, people are doing that already. But I think this is a situation where we may not be able to necessarily use, at least not exclusively, adult data to inform the pediatric data because most patients who are adults getting implants already have language and social skills and they're educated, whereas the children in that same audiometric range do not necessarily have those things. So this is a situation where we could start with the adult data that we have. And as we talked about, I don't know how much we have, but I think there is definitely a need for additional work, prospective work.

DR. WOODSON: Yes, Dr. Eydelman.

DR. EYDELMAN: Sorry, if I can interject. As we're listening from the Panel members,

I was hoping that each of you can actually recommend a particular level that you would be comfortable with, because what the question -- since you no longer see the preamble to the question, it was whether the change in indication can be done without the preclinical data. So, based on something we're going to do postmarket, how much of a change do you feel comfortable with?

DR. WOODSON: We would like people to recommend a specific dB level.

DR. EYDELMAN: Yes, please.

DR. WOODSON: And you said 80 and --

DR. MADELL: Can I change it? I'd like to change it to 75.

DR. WOODSON: Okay. Dr. Nelson, do you have a recommendation?

DR. NELSON: Well, not quite yet.

DR. WOODSON: Okay.

DR. NELSON: You know, I'm open to that, but I don't think I know the answer, and I wonder if we could ask Dr. Gifford to respond.

DR. WOODSON: Okay.

DR. NELSON: Would that be appropriate?

DR. WOODSON: Yes.

DR. NELSON: And some of the cases that she was talking about were in a case of severe loss bilaterally, but asymmetry --

DR. WOODSON: Yes.

DR. NELSON: -- where the poor ear was still not necessarily a candidate for implantation. So there's some -- yeah.

(Off microphone comment.)

DR. NELSON: Not necessarily, I think.

DR. WOODSON: Okay, Dr. Gifford.

DR. TOMBLIN: Can I interject, because she might have comments on this, as well?

DR. WOODSON: Okay.

DR. TOMBLIN: Because this is a topic that's gone on in my lab, although I'm not --

DR. WOODSON: Dr. Tomblin is speaking.

DR. TOMBLIN: Tomblin, yes.

Why couldn't we consider aided SII as opposed to pure-tone average, unaided pure-tone average?

(Off microphone question.)

DR. TOMBLIN: It's Speech Intelligibility Index. That is, we can take a child, unaided -- we can take a child and say this is what we could get probably best from a hearing aid and from that know then -- and that sort of takes into account some of the issues that Jane's talking about with regard to configuration and so forth. And we could say, well, this child -- we know that children with this kind of aided SII generally have these kinds of outcomes. Now, the tricky part is you can't get an SII directly on children with cochlear implants, but at least that seems to me to be -- at least puts things on the comparison to say, well, this is the kind of speech intelligibility a child could get and then we could go from there. I don't know. I'm not an audiologist, so --

DR. WOODSON: Let's hear Dr. Gifford's recommendations.

DR. GIFFORD: René Gifford.

I think there's another level, too, beyond this. Rather than just throwing out numbers, 70, 75, 80, the thing I want to bring to the table here is keep in mind that detection thresholds are just that, they're detection. It's a very low-level form of processing. And what children need to be able to do is perception, which is very -- that happens at the level of the brain. And, you know, in animal studies, how many neurons do you need for detection? One. But we know that one is not enough to give a child what they need in order to learn language.

So I think that even though these are fantastic recommendations, I would be remiss if I didn't say I don't know that you want to set a specific criterion as far as like, okay, every child has to be 70 dB HL or worse. I think it really needs to be more ear specific and based on their functional capabilities with what they do with that hearing, because recall, detection is just detection.

DR. WOODSON: How would you determine that function?

DR. GIFFORD: I'm sorry, which function?

DR. WOODSON: Yeah, how would you document that function?

DR. GIFFORD: Oh, it would be on the basis of the team input, like Dr. Madell said. You know, what does the speech-language pathologist say to the auditory verbal therapist? Is the child making month-for-month growth in auditory and speech and language development? For the older child, is the child reaching a criterion level of speech understanding in quiet and at multiple levels as well as in noise? Is the child FM dependent? All of these things that are really sort of looking at the true auditory profile and the functional capabilities of the child versus just an audiometric threshold, which is

just a very small piece of the puzzle.

DR. WOODSON: Let's go around this way a little more, and then we'll come back to you.

DR. NANDKUMAR: Part of her recommendation is in No. (ii) there also, preoperative speech recognition scores.

DR. WOODSON: Okay, Dr. Ishiyama.

DR. ISHIYAMA: For very young kids, I think once we know that the child is profoundly deaf and that is confirmed with behavioral testing at age 9 months, these kids should be implanted. These are kids with bilateral profound sensorineural hearing loss.

DR. NORTON: So I do believe that -- I can't keep things straight. But for one of the manufacturers, severe loss of 70 dB and greater is already approved at 18 months. And for MED-EL, I mean, it doesn't put any restrictions on your thresholds below 1,000 Hz with the current approval criteria, and that is 12 months and above. I think that if we're going to look at this in terms of -- an SII is one thing. It doesn't always agree with speech understanding performance in older children, but in your garden variety of hearing loss, it does. But the decision to do early bilateral implantation at 6 to 9 months based just on an audiogram in a child with 90 to 100 dB thresholds where -- I've never seen anyone achieve, in my 40-year career, good speech on auditory alone, speech and language, with that degree of hearing loss with hearing aids.

(Off microphone comment.)

DR. NORTON: Yeah, they're not an issue. What we're talking about is those very -- how low do we want -- how low do you go, how young do you go for the severe hearing loss

group?

DR. BRIETZKE: I think I'm uncomfortable going with one number. It really is a decision based on many factors. And I think the parent motivation is another huge factor and then developmental abilities of the child. We can't regulate clinical judgment, which is what the group is trying to do here. We can maybe provide a starting point, but there has to be an element of judgment involved.

DR. WOODSON: Do you have any comments about a number?

DR. TOMBLIN: I don't know. Yeah, I agree, the difficulty here is that we are getting into a gray area, and it's very hard, I think, then to put a discrete number on something that is going to be wrong some of the times and not wrong the other times. If somehow one could come up with, just for me, something that would be graded like a probabilistic thing or something, then maybe we could handle the gray. But I think that 90 dB is outside the gray area. From my experience and so forth and particularly working with children with hearing aids, 75 dB may be at the other side or maybe even a little more, but somewhere in there, maybe on the other side of the gray, but there's that gray area, and how to handle that is tough.

DR. WOODSON: Yes, Dr. Hirsch.

DR. HIRSCH: I don't do kids, but I'll throw out numbers. So the first thing we have to say is that they're not progressing with growth on hearing aids. Can we all accept that?

DR. WOODSON: Yes.

DR. HIRSCH: And that's every company's criteria. Some demand hearing aids and some recommend hearing aids, so there is variability amongst the companies. But that

should be number one.

The other thing we went through with the Hybrid was trying to come up with numbers also. And we actually came up with numbers, so let me just throw this out for discussion. Let's say we set a PTA of 75 and then define the frequencies of 5, 1, 2, and 3. That would take kids who have got severe to profound loss. Typically, it's 1,000 and above, so they're hovering at that 90 dB level. But even if they were at 75 across, at 1,000, 2,000, 3,000, and they did not show growth with hearing aids, they could be considered cochlear implant candidates. So I'll throw that out as a number, if that's what you're looking for, a number, as opposed to saying moderate to profound. You know, moderate, that's 70 -- a little less than 70, and profound would be 90 and greater in the higher frequencies. But I'll throw that out as a starting point.

DR. WOODSON: Sujana.

DR. CHANDRASEKHAR: So I'm going to counter your numbers with some other numbers because the question is -- the top of the question, that we can't see, is can we extrapolate postmarket -- premarket to postmarket with the premarket data being the adult data? So the adult indications are 60 dB or worse thresholds and 50% sentences and 60% best-aided sentences. So I think the question we're being asked is can we say we can extrapolate the adult criteria to pediatric criteria, given that children also need to prove to us that they're not advancing in their language, that their best-aided condition is not making them better? But that's actually a much better level of hearing than we've talked about, but that's the level of hearing we're implanting in adults right now.

DR. HOUSTON: I don't think we can use the adult criteria -- well, at least with very

young children, simply because they cannot do a sentence recognition task.

DR. WOODSON: I would agree with that.

DR. HOUSTON: You can give pure tones, but you can't meet all of the criteria for the adult because you can't find out what their sentence recognition is.

DR. WOODSON: Marly.

DR. KENNA: And I agree. Earlier, I think we said that you can't extrapolate the adult data in this particular situation. But to me, although we sort of acknowledge that, in general, implants are very safe, I think -- and this is a group of children who actually with appropriate hearing aids might never need an implant. And so safety becomes, to me, a little bit more of an issue than in a child who's 90 in both ears, and we know really we will not likely make good progress in spoken language acquisition. So this, to me, safety bumps up against -- it enters the conversation anyway.

DR. WOODSON: Dr. Nelson.

DR. NELSON: So I think we're all -- it feels like we're all saying that the 90 dB bilateral is more strict than we would like. We're hearing data that suggests that there are more children than that who could benefit from cochlear implantation at an earlier age and that that number right now is pretty severe. Now, I was going back from what Susan said, to look at the criterion. So Cochlear's seems to be -- it says once children are at 2 years, it may be severe or profound bilaterally.

So is there a ground for us where we can kind of support that at a younger age, that if there's a severe to profound loss even in the early ages and they are not benefiting from acoustic information in a systematic, month-to-month tracking of their auditory abilities,

that the FDA would get behind a standard on the label, implantation of those younger children with severe to profound loss? But I'm not ready -- it sounds like a very reasonable number, but I don't know that -- you know, I'm not ready for it yet.

DR. HIRSCH: Severe is 70. So you're going up a little bit, severe to profound. So somebody could be coming in at 72 across the board and make criteria there.

DR. WOODSON: What I'm hearing is that people are not comfortable with making a life-long decision for the child to have an implant, given the fact that you're not that comfortable that 70 dB means they're not going to do well. So I think that we can't really just take the adult, but it sounds like if you -- maybe at the level of 70 or something and they don't make progress, then everything has to be qualified by not making progress with good hearing aids.

DR. ISHIYAMA: I think I'm not sure whether I made my points clear or not, because I think we're talking about two different groups. Because of the enforcement of newborn screening, we have a set of kids that we are identifying very early on. And the data that Niparko showed, and also the one that Advanced Bionics showed, clearly shows that if you implant the child younger than 12 months of age, there is a tremendous benefit. So I think once we can be sure with behavioral testing -- and I think 9 months is a very reasonable timeline to draw for kids with thresholds of 90 dB or greater. For example, MED-EL has 1,000 Hz. These kids probably should be implanted. And then there's another group of kids who make no progress with the use of hearing aids and I think --

DR. WOODSON: So there are two bars, then.

DR. ISHIYAMA: Yes.

DR. WOODSON: There's the absolute bar and then this bar with no progress.

So you had a comment?

DR. TERRIS: Yes. I mean, what everybody can hear is uncertainty. Lack of consensus around this issue is what I'm hearing, and I'll just point out the reality, which is if you reduce the threshold, more kids are going to get implanted, whether or not we know it's better for them or not. And especially, as Marly pointed out, there are safety concerns and maybe it's not the best thing for them, but what's going to happen is more kids are going to get implanted. So that's a concern for me.

DR. ISHIYAMA: I think, you know, for the benefits of kids with profound hearing loss -- I'm talking about very young kids, younger than 12 months old. Once we are absolutely sure the diagnosis is correct, again with behavioral testing, I see absolutely no harm and I think it's detrimental to hold those kids back than going ahead and doing the implants.

DR. WOODSON: So you have a motion -- well, let's hear from Dr. Houston.

DR. HOUSTON: I think a dilemma we're having right now is that we're much more comfortable with numbers that you would get from an audiogram than this idea of not progressing. But not progressing, I think a lot of us are saying, is more important than the actual audiogram.

DR. WOODSON: I think that's not exactly right. I think we're saying we're not comfortable with numbers in the gray zone, in the way bad --

DR. HOUSTON: Yeah.

DR. WOODSON: -- 90 dB or something. We trust the numbers. But when we get a little higher, we want to make sure that they don't benefit from hearing aids.

DR. HOUSTON: Okay. I mean, I guess I would say I would be -- if we're basing it on audiograms only, I would only be comfortable down to about maybe 80 dB. But if we're basing it mainly on progress, I'd be fine with going all the way down to 60.

DR. WOODSON: Yes.

DR. MADELL: I think part of this is that one of the cochlear implant companies has, as a criteria, between 12 and 24 months you have to have a profound loss, but over 24 months you can have a severe loss. I can't imagine a justification for why a child has to hear more at 2 than they do at 1 or at 6 months, which is what they really need to have.

DR. WOODSON: So are you proposing that that criteria should be a good --

DR. MADELL: I think it should not be by age.

DR. WOODSON: Yeah.

DR. MADELL: It should all be degree of hearing loss. And I would say, if we have to do a PTA, I would do 1,000, 2,000, 3,000, not include 500 where you might have better hearing. But I would like to propose that we consider severe hearing loss and not making sufficient progress as the criteria.

DR. WOODSON: And what about profound?

DR. MADELL: Severe or profound.

DR. WOODSON: But maybe he said profound -- he was saying that you don't want to sit around and wait. If you know they have a 90 dB hearing loss, you don't want to sit around and wait, is what he's saying, whereas if it's more in the severe range, you want to -- is that -- Sujana.

DR. CHANDRASEKHAR: Sujana Chandrasekhar.

But, you know, the point that was made earlier was that even -- Marly brought it up -- are we delaying this child's access to hearing information by doing a hearing aid trial for 3 months in these profound kids? And the reality is most of them have some hearing, and putting powerful hearing aids on them gives them access to something and we can -- you don't implant children in isolation of everything that goes on around them. You implant them within their family structure, within their education structure, within their early intervention program, within everything else. So it's not unreasonable for a profound child to put a pair of hearing aids on, and then after a month, if there's really nothing, I think you've done a reasonable trial. But for the severe child, to do a full 3-month trial makes a lot of sense. And I think that's the very good judgment of any good audiologist.

DR. ISHIYAMA: I think the question is, if you have a 9-month-old kid, how would you tell the difference whether you're making progress or not in 1 month, 9 months, and 10 months? I think we're clearly talking about two different groups. So I think when a child is born with a profound deafness 90 dB or greater and that's confirmed with behavioral, these kids need to be implanted at the young age, 9 months.

DR. TOMBLIN: I guess a point of information. My concern with this, it is sort of the joint problem of reducing the age and the severity. But a lot of that concern gets back to the issue of safety or we could say maybe the degree to which we can have confidence that we do indeed know what this child's hearing is like. And I'm pretty sure that knowing that before 6 months gets to be kind of tricky. And even later. So I guess it has to do with the confidence interval that we have. And as we drop the guidelines down for severity, and then as we go down in age, the confidence interval expands, it seems like we come up to a

point where there's a reasonable chance that we might be implanting a child with pretty decent hearing who might do well with a hearing aid. And so that's really the battle that's going on in my mind.

DR. WOODSON: So the question is do we say no, we don't think you should implant children this age, or that we should try it and do a postmarket study to see if it worked? I mean, that's the basic question.

DR. ISHIYAMA: May I ask a question? Can we ask the presenters, from the guest speakers, what the opinion is? Because I want to know. My specific question is, do you have any concern once the child is identified to be profoundly deaf, 90 dB or greater, with behavioral testing demonstrating no hearing? Do you have any objection to recommend implantation?

DR. WOODSON: So who do you want to address your question to?

DR. ISHIYAMA: Dr. Gifford and -- I'm sorry, I don't know your name -- from Boys Town.

DR. GIFFORD: René Gifford.

If we have documented that the child has behavioral hearing, profound or worse, I have absolutely no qualms whatsoever about recommending bilateral cochlear implantation. So I think your question is, for under 12 months, if that has been documented. Absolutely.

(Off microphone comment.)

DR. GIFFORD: Including behavioral testing.

DR. ISHIYAMA: I'm sorry, Dr. Hughes.

DR. HUGHES: That's okay. Yes, I completely agree with Dr. Gifford on that.

DR. HIRSCH: Barry Hirsch.

But those are accepted criteria.

DR. TOMBLIN: I guess I'm more interested in the child that has severe loss. Let's say a 6-month-old who, if truth be known, had a hearing loss of -- let's make it 70 dB to make it really hard. What's the confidence interval around that for our estimates of what the child's threshold would be?

DR. ISHIYAMA: I think Barry said it's already accepted. It's not. I'm saying drop it to 9 months or 12.

DR. CHANDRASEKHAR: So the question is what happens with the 10- or 12-month-old that you can get pretty accurate thresholds that are at 70 dB? And that child who fails or does not -- we can't say fail anymore -- does not progress with hearing aids, that child, I believe that this Panel thinks, is a candidate for cochlear implantation.

DR. WOODSON: Does anyone disagree with that?

Marly.

DR. KENNA: This is Marly Kenna.

I'm not saying I disagree, but I think all of us who see these children, there are some you put hearing aids on them and they take off, and that's the last you see of them in terms of the cochlear implant discussion. So I think if those children are doing very poorly, absolutely, implanting them would be a really good idea. I think it's just how to figure out who those kids are and not to implant them automatically. I think that's my main concern.

DR. WOODSON: Are you including the 90 dB?

DR. KENNA: No, the 90 dB kids --

DR. WOODSON: Okay, okay.

DR. KENNA: -- to me, that's a no-brainer.

DR. WOODSON: So we have an absolute --

DR. KENNA: Yes.

DR. WOODSON: -- level around 90 dB, and then we have maybe 70 dB or so where you would use the criteria.

DR. KENNA: Right.

DR. WOODSON: I think we're really getting kind of bogged down, but that seems to be what people are crystallizing. We'll have a couple more comments.

Yes, Derek and then Sujana.

DR. HOUSTON: I'm starting to picture like a graph where you would have level of hearing loss and the duration of the hearing aid trial. Like, the greater the hearing loss, 90 dB, no hearing aid trial. Eighty decibels -- or maybe 1 month. Eighty decibels, 2 months. You know, whatever it would be, that there would be a graph that, you know, the candidate -- the patient would need to fall on one side of this line to meet FDA approval. I don't know if something like that would be possible, but that's what I'm starting to picture.

DR. WOODSON: Okay, Sujana.

DR. CHANDRASEKHAR: Sujana Chandrasekhar.

I think that Dr. Madell's suggestion of severe to profound without progression with hearing aids is the question that we're all being asked to look at, and can we extrapolate the adult data enough to expand pediatric indications.

DR. WOODSON: I don't think the idea is that we're extrapolating adult, because we've agreed that it's not the same. But we're saying --

DR. CHANDRASEKHAR: Can we expand --

DR. WOODSON: -- can we use a postmarket study to determine this?

DR. CHANDRASEKHAR: Correct.

DR. WOODSON: Do you think you have enough information, Dr. Eydelman?

DR. EYDELMAN: More than enough.

DR. WOODSON: Okay.

(Laughter.)

DR. WOODSON: All right, because that seems to be our toughest question, I hope.

All right, now the pre-op speech recognition scores. We have discussed a bit about the fact that they just don't apply to babies.

Does anyone have any thoughts about using speech recognition scores?

(Off microphone comment.)

DR. WOODSON: Huh?

(Off microphone comment.)

DR. WOODSON: I know, but what's the question?

DR. PENG: Can I clarify?

DR. WOODSON: Okay.

DR. PENG: By speech recognition scores, I think it may be better to take into account the parental questionnaires, like IT-MAIS and MAIS, to be brought because we are talking about the younger, so we intend to exclude those kind of scores. We are just talking about

any functions.

DR. WOODSON: Yes.

DR. PENG: Functional hearing. Yeah.

DR. WOODSON: So we think that speech recognition scores -- you're asking us if they're relevant.

DR. PENG: Because the current approved indications for all three manufacturers, they are all proposing the speech recognition scores.

DR. WOODSON: Um-hum.

DR. PENG: But if we extend this to younger kids, it may not be -- yeah.

DR. WOODSON: Because you can't collect the data. So we should say --

DR. NANDKUMAR: And I think you all covered it --

DR. WOODSON: Yes.

DR. NANDKUMAR: -- by using the functional and behavioral.

DR. WOODSON: Yeah, okay. So --

DR. NANDKUMAR: I think we can move to the next question.

DR. WOODSON: We can move to the next. Okay. So then, gosh, asymmetrical loss or single-sided deafness.

(Off microphone comment.)

DR. WOODSON: Yeah.

DR. NELSON: I mean, I think we have seen that there aren't enough data on single-sided deafness.

DR. WOODSON: Okay.

DR. NELSON: I did have a question for Dr. Gifford because I thought I interpreted that, even in cases of asymmetrical loss, they're not technically bilateral, profound. So is there some gray area there that we should be discussing?

DR. WOODSON: She made the point and we can ask her to reiterate that she thinks it's better to go by testing that ear, and even if the other ear seems like it's pretty good, they still got better. That's what her data shows. So I guess the question is do we think we have enough data to say that, or at least to have it looked at postmarket?

Dr. Madell.

DR. MADELL: Jane Madell.

I think we need to look at asymmetrical and single-sided deafness separately. They are really not the same. And with asymmetrical hearing loss, we should be looking at each ear separately. The data on bilateral -- binaural hearing is very clear. People do much, much better when they have two ears. So we need to be looking at each ear separately and a child may have -- not necessary to implant one ear and another ear that would benefit from an implant. And in the past, people have said, if you've got a better ear that's not implantable, neither ear is a candidate. And I think that's something we need to reconsider. We need to look at each ear separately, and if one ear is an implantable ear, we should implant that ear even if the other ear is not.

DR. KENNA: This is Marly Kenna.

I completely agree. I mean, people with asymmetric hearing loss, by definition, have hearing loss in both ears. So that's a very different patient population than the 3-year-old who has normal hearing in one ear and severe to profound hearing in the other ear. To me,

that's a very different patient. And so we certainly do not have the data, I don't believe, for that second group.

DR. WOODSON: Crystallize your recommendation.

DR. KENNA: So I think my recommendation is that we have -- as Dr. Madell was saying, I think we have probably enough data from Dr. Gifford's studies and other studies to say that we can go forward with implantation, looking at each ear separately for asymmetric hearing loss. I really don't think we have that in children for single-sided deafness --

DR. WOODSON: Okay.

DR. KENNA: -- when they truly have normal hearing on one side and severe to profound hearing in the other.

DR. WOODSON: Okay, Susan.

DR. NORTON: Well, I think we have to look at the degree of hearing loss in the non-implanted ear because there are kids with mild to moderate hearing loss or low-frequency hearing loss in the better ear. And there's a very slippery slope about what constitutes unilateral hearing loss if you have a mild hearing loss in one ear and a severe to profound loss or a steeply sloping loss in the other ear. So I'm not sure this one is as cut and dry for me. I mean, we look at each individual case, and it's a difficult decision.

DR. ISHIYAMA: I think I agree with Dr. Madell's comment completely. And I would like to ask one additional question to the guest speakers. To all of them, actually. If you have a down-sloping hearing loss, current FDA criteria for the Cochlear implant, for Hybrid, is 18 years of age. That was the cutoff. Now, if you have kids who are not doing well with

hearing aids, what will be your concern to implant these kids? I want to hear your opinions.

DR. CHANDRASEKHAR: This is Sujana Chandrasekhar.

So these children, if they were adults, would be Hybrid candidates. So the children with a Hybrid type of hearing loss, do you guys have concerns about implanting under 18 with that type of hearing loss?

DR. HUGHES: This is Michelle Hughes.

I think the one thing that hasn't really been talked about here is, are we making assumptions, in the pediatric population, that their hearing is never going to progress?

DR. WOODSON: I don't think --

DR. HUGHES: I'm sorry, that was the question I had answered.

DR. GIFFORD: René Gifford.

I'm going to probably sound like a broken record here, but I have no concerns about that patient population because actually some of the children in the study with the 51 children were that hearing loss. I recall one little 4-year-old who had normal hearing at 125, and then by the time she got to 750, she was profound. We implanted her. She was not making progress that she needed with hearing aids. I mean, aside from all of this, she had hearing preservation, but that was not the goal of that surgery. With just electric alone, her language development and her auditory skills just took off after she got implanted. So that's why I was reluctant earlier to really put a hard number on it, because someone like that who has technically normal hearing at one frequency would not necessarily meet even these new indications.

DR. HIRSCH: And, René, what was the other ear? Were they similar?

DR. GIFFORD: In that particular child, she was symmetrical. Yeah. And then actually, in the other ear that was not implanted, she did start to lose some hearing. So that hearing was progressive. Like Dr. Hughes had said, a lot of times these types of losses in children tend to be progressive.

DR. BRIETZKE: This is going to what something Dr. Kenna said about single-sided deafness. We clearly have the data from adults, but even when we do, it's probably not going to be applicable to children. When we look at the etiology for single-sided deafness in children, it's almost exclusively very different. So this is a particular indication where we really can't extrapolate even when that data is available. An important point.

(Off microphone comment.)

DR. BRIETZKE: Probably a different story. I mean, when we look at what would cause asymmetric -- single-sided deafness in a child, it's going to be cochlear abnormalities. Malformation is a completely different story, whereas with asymmetric it's probably going to more applicable.

DR. WOODSON: Dr. Ishiyama.

DR. ISHIYAMA: Yes. For the single-sided deafness, I agree with you completely, the data isn't out there yet. But for kids who could possibly benefit from Hybrid type of situations, I think we need to include children who are not making any progress with the use of hearing aids. So I think that should be included --

DR. WOODSON: Okay.

DR. ISHIYAMA: -- because we know for certain that, with the 422 electrodes, we can definitely preserve the hearing in the low frequencies. So there's no harm then.

DR. WOODSON: Dr. Tomblin.

DR. TOMBLIN: It's Tomblin.

I think I am leaning toward or seem to be in concurrence that for the unilateral losses, we just don't have the data, and even in adults. The children -- recognizing that it's still somewhat ambiguous about the degree of the asymmetry, the asymmetrical losses sound like they could be justified.

DR. WOODSON: Dr. Houston.

DR. HOUSTON: I agree.

DR. WOODSON: Sujana.

DR. CHANDRASEKHAR: Sujana Chandrasekhar.

I agree and I think bilateral asymmetric hearing loss, even at a mild level, we put hearing aids on children with mild hearing losses to encourage optimal educational outcome. And I also agree that there's not enough data on single-sided deafness.

DR. WOODSON: Dr. Hirsch.

DR. HIRSCH: Barry Hirsch.

I agree about the single-sided deafness. If the other ear is normal, that deaf ear should not be implanted. But I have trouble in defining, as Susan was saying, to what degree is that other ear mildly affected by hearing loss. So if you have a kid coming in around 20 dB or maybe 40 dB where a hearing aid does really well, I have some -- I'm uncomfortable with doing an implant in that. I just don't know where the kid is going to go.

DR. WOODSON: So you're talking about a mild loss in one ear and a severe loss in the other, you wouldn't implant the severe. Okay. So we don't have complete consensus,

but the majority opinion is bilateral yes, unilateral no, asymmetric probably.

DR. EYDELMAN: Terrific.

DR. WOODSON: Okay.

DR. ISHIYAMA: Please include the Hybrid type of situation, meaning down-sloping hearing loss --

DR. WOODSON: Down-sloping hearing loss.

DR. ISHIYAMA: -- who cannot make any progress with their hearing aids.

DR. WOODSON: Yes. So they have, yes, someone who's not making progress.

Sujana.

DR. CHANDRASEKHAR: And I'm sorry to say, but I think number five on this list is age, because we have talked about reducing the age of indication. So I just added it myself because we've been talking about 9 months, 6 months, some months, and I think we have consensus that 12 months is arbitrarily too late, and I'm hearing that many of the panelists want that younger.

DR. WOODSON: Okay, I'm going to ask for a show of hands. Is 12 months too old for a cochlear implant? For the minimum age.

(Count.)

DR. WOODSON: Okay, what about 9 months?

DR. HOUSTON: Is that too old?

DR. WOODSON: Is that too old?

DR. HOUSTON: Yeah.

DR. WOODSON: So what age would you propose?

DR. HOUSTON: Six months.

DR. WOODSON: Six months. So what do the surgeons think?

DR. BRIETZKE: There's definitely some limiting factors here. And we talked about this, this morning. I mean, it's the skin thickness, and you're putting a magnet on that skin every day for hours at a time. There are limits, and there will be exclusions for sure. I've seen it when I do young children, so it happens. It has to be factored into that.

DR. ISHIYAMA: I think I'm not too concerned about that because if you're --

DR. WOODSON: Say your name every time you speak.

DR. ISHIYAMA: Ishiyama.

If you have a child with a very thin thickness, you could consider swinging over a TPF flap and provide extra coverage. So that's not the issue that I'm concerned about. What I'm concerned about is whether you can definitely, without any correction, establish the presence of profound hearing loss.

DR. WOODSON: So what would be your age limit recommendation?

DR. ISHIYAMA: Nine months.

DR. WOODSON: Nine months.

DR. ISHIYAMA: Because I don't really think we're going to do much difference by pushing it all the way down to 6 months.

DR. WOODSON: Okay. Who votes for 9 months?

(Count.)

DR. WOODSON: Okay. We're saying that 9 months will be the lower limit of what we would recommend.

(Off microphone comment.)

DR. WOODSON: Put your mike on. And this is Dr. Madell.

DR. MADELL: Jane Madell.

I just want to say that, just for a piece of information, in Australia the standard is at around 3 months. Piece of information. Many centers are implanting at around 20 pounds when the anesthesia risk is reduced, and that is usually 6 to 7 months in many --

(Off microphone comment.)

DR. MADELL: It's not? What is it?

DR. KENNA: This is Marly Kenna.

Just a point of information. Many of our 1-year-olds weigh less than 20 pounds, so I would not use weight. I mean, it's a concern in terms of blood loss and anesthesia, but I wouldn't use weight as a defining factor.

DR. MADELL: Okay.

DR. WOODSON: So I would like for the people who were --

DR. MADELL: I was going to say 6 months, if we have the information.

DR. WOODSON: This is the Chair. I'd like the people who are surgeons, who actually do the surgery, to raise your hands. And leave your hand up if you think 9 months is the correct age.

(Count.)

DR. WOODSON: Okay. Any of you think that 6 months should be correct?

(Count.)

DR. WOODSON: No. And those are the guys that are putting them in. So 9 months

is our consensus.

Okay. So let's see. This is --

(Off microphone comment.)

DR. WOODSON: Huh?

DR. NANDKUMAR: You have Part (c).

DR. WOODSON: Part (c) means is there anything else?

DR. NANDKUMAR: Yeah. So you just discussed it.

DR. WOODSON: That was it, okay. That was the other thing. All right.

So it is now 3:30. We had a break that was scheduled at 3:45. I think if we get a little refreshment from heaven, a little 15-minute break, and then we'll start again and start afresh with Question 2. And start thinking in your mind while you're on a break, although you can't discuss about what your thoughts are.

(Off the record at 3:30 p.m.)

(On the record at 3:48 p.m.)

DR. WOODSON: All right, we're going to begin the last session. We're going to have a point of order from our Lieutenant Commander.

LCDR GARCIA: Thank you, Dr. Woodson.

This is Patricio Garcia, Designated Federal Officer. As a point of order, I have been asked by the transcriptionist to please use your microphones, and even though some of these conversations have been a little bit passionate, try not to talk over each other. Other than that, I think we're having a pretty good discussion.

Thank you.

DR. WOODSON: All right, now we're going to Question No. 2: It may be possible to support reasonable assurance of device safety and effectiveness by extrapolating data from one age subgroup to another for certain cochlear implant device modifications. Given the patient and device characteristics, please discuss the following:

a. Please discuss whether data from adult clinical trials are suitable for extrapolation for the premarket approval of advances in cochlear implant technologies in older pediatric populations (e.g., age 6 and older).

DR. WOODSON: So who would like to lead off this question?

DR. HIRSCH: Barry Hirsch.

I agree.

DR. WOODSON: Okay.

DR. CHANDRASEKHAR: I'm Sujana Chandrasekhar, and I agree.

DR. WOODSON: Does anybody disagree?

(No audible response.)

DR. WOODSON: Okay, next -- oh, sorry. Okay. We're going too fast for you. I'm sorry.

DR. NORTON: You are.

DR. WOODSON: Susan, okay.

DR. NORTON: Susan Norton.

So are we asking just about the external device, or are we asking about major changes to the internal device?

DR. NANDKUMAR: So this is a question about extrapolation, not the premarket/post

shift. This is more whether adult data can be extrapolated, all the kid data, for all, any and all changes. We're not differentiating between them.

DR. NORTON: I would vote for external, but I would not say that the safety and efficacy -- I do not agree that the safety and efficacy of significant modifications to an internal device can be extrapolated down.

DR. WOODSON: Scott.

DR. BRIETZKE: We just spent a lot of time talking about, you know, single-sided deafness. I think it's possible -- the question is worded "possible," yes, but it depends on the question. I think there are some facts that have to be looked at.

DR. KENNA: Marly Kenna. I just have a question.

Are we just talking about the hardware in this question? I guess that's the question. Is this hardware, or we're talking about data? They're two totally different questions.

DR. NANDKUMAR: We're talking about hardware and indications, any changes. But here, we're not talking about your prelingual younger -- we're just talking extrapolation from adults to the older kids, older children, who may have the same kind of reporting abilities as the adults.

DR. WOODSON: Dr. Tomblin and then Dr. Hirsch and then Dr. Nelson.

DR. TOMBLIN: Just, for instance, because this is what I need. If the internal device is changed such as now you go to a short electrode, right, is that the kind of change that could be in this, that it -- you know, it's -- because that, I guess, could be -- and I guess then it's -- so, anyway, would that be one of the kinds of changes?

DR. NANDKUMAR: I think we were focusing here mostly on cochlear implant, not

the Hybrid, if that's what you're thinking of.

DR. TOMBLIN: Yeah. Well, Hybrid or short.

DR. NANDKUMAR: The focus here was mainly on the cochlear implant.

DR. TOMBLIN: The long -- the standard.

DR. NANDKUMAR: Yeah, standard. Severe to profound hearing loss.

DR. TOMBLIN: Okay.

DR. WOODSON: Dr. Hirsch.

DR. HIRSCH: I think that has to really be specified because the current criteria for the Hybrid says 18 and above, and if you extrapolate this stuff to kids, even 6 and above, you don't know the stability of their hearing pattern even at that age.

DR. NANDKUMAR: That's good input.

DR. HIRSCH: So that Hybrid should be taken off the board.

DR. NELSON: Peggy Nelson.

I was just interpreting this. It says reasonable assurance of device safety and effectiveness. So if we're talking about standard cochlear implant arrays, standard cochlear implant signal processing, reasonable assurance of device safety and effectiveness, then yes. Then I vote yes for that.

DR. MADELL: So are you saying that we should -- that Hybrids -- are you saying Hybrids should not be -- Jane Madell, sorry.

Are you saying Hybrids should not be implanted in children, that there's -- that we're not saying that there's a case for implanting Hybrids in children?

DR. HIRSCH: I'm saying that Hybrids should not be implanted in children yet because

there's still no long-term data on adults. So far adults are only entitled to get one ear. The long-term results of further hearing progression is not really out. In the initial study there was about 40% hearing loss in the Hybrid adults. So if you take a kid who's destined to have progressive hearing loss in the low frequencies also, may have an electrode in them that is too short, they're not covering the apical end. So yes, I'm saying not to do it.

DR. MADELL: I don't disagree. I just was trying to understand.

DR. WOODSON: So let's -- this is Dr. Woodson. Let's clarify from the FDA the question.

DR. EYDELMAN: So the question was left wide specifically so that Dr. Hirsch could make his comment and we can take it into consideration.

DR. NANDKUMAR: I think we have information for this.

DR. WOODSON: All right. So the conclusion, then, is that external modifications are fine, but not change it to the implant array itself.

DR. NANDKUMAR: I think -- no, I think it's based on the indications, I think.

DR. WOODSON: Indications?

DR. MADELL: Particularly as it relates to Hybrid.

DR. WOODSON: Hybrids, okay.

DR. MADELL: Because they're short electrodes.

DR. WOODSON: Yeah. You have the information you need?

(No audible response.)

DR. WOODSON: Okay. Yeah. And, again, make sure you state your names.

The next, part (b): Given the characteristics of the younger pediatric population

(e.g., younger than age 6), such as lacking hearing in spoken language experience prior to implantation and limited reporting capabilities, please discuss the type of premarket clinical data (e.g., adult, older children) that might be suitable to support a premarket to postmarket shift in clinical data requirements for approval.

Would someone like to restate that question?

So children don't have the language skills, so the types of tests that we use that relate to language skills are not appropriate. So what type of data from adults and older children are suitable to use for the younger child?

DR. CHANDRASEKHAR: This is Sujana Chandrasekhar.

There are language tests that are in use, and in the slide that was shown from Nashville, they showed -- and again, later, it showed the increased complexity of those testing from less complex to more complex, which is how we expect these children to progress as they continue to hear and use language centers. So my interpretation is that we've talked about this a lot and we've already had this discussion. I don't know if FDA is --

DR. WOODSON: But we talked about what tests are useful in very young children, but the question here has to do with taking -- you don't do those really young children tests in the adults and the older children, right?

So Susan.

DR. NORTON: Susan Norton.

So I think this means if older children and adults show improvements in speech understanding with a new speech processing algorithm, can that be extracted to younger children who cannot respond?

DR. NANDKUMAR: Yes.

DR. NORTON: So that kind of data changes to the speech processing strategy can be extrapolated to younger children. Changes -- I think we've already answered this question.

DR. WOODSON: Okay.

DR. NORTON: Changes to front and pre-processing cannot be extracted to younger children who cannot provide feedback.

DR. WOODSON: Okay.

Is that adequate, Dr. Eydelman?

DR. EYDELMAN: Yes.

DR. WOODSON: Okay.

Please discuss specific considerations that need to be addressed when using data from adult or older pediatric patients to support safety and effectiveness in pediatric patients, younger than 6 years of age (e.g., age of implantation, developmental and cognitive factors, pre/postlingual onset of severe-to-profound deafness, severity of hearing loss, etiology).

We covered some of this when we talked about the age of implant, and we talked about the levels. We discussed a little bit about pre- or postlingual onset.

Yes?

DR. MADELL: Jane Madell.

I think that we sort of touched on this when we talked about the short electrode. We know that children, a significant number of children have progressive hearing loss, something more than 50% of kids have progressive hearing loss. So we need to be sure that

whatever a child is implanted with is something that will be able to be modified should the child's hearing get worse.

DR. WOODSON: Does anyone have any comments about that, agree or disagree?

DR. ISHIYAMA: I agree with that completely.

DR. WOODSON: Are there any other considerations that someone would want to bring forward?

(No response.)

DR. WOODSON: Is that adequate?

(No response.)

DR. WOODSON: Okay, No. 3: Please discuss the scientific/clinical relevance of the following types of data that have been used as supporting evidence for premarket approvals of device modifications for cochlear implants in PMA supplements:

a. Unpublished adult and/or pediatric clinical data collected from prospective, outside of United States (OUS) studies.
b. Published findings from retrospective studies on data obtained from pediatric patients.
c. Prospective or retrospective clinical performance data obtained from a subpopulation of pediatric cochlear implant recipients (e.g., children at a relatively older age, such as 6 and older or 12 and older).

DR. WOODSON: Marly, you want to comment on that?

DR. KENNA: Sure. Yeah, this is Marly Kenna.

So I think obviously sometimes this is all the data we have in some of those

categories, so whether you can use it or not, I think depends a lot on the quality of the data, how it was collected, consistency of the data, whether you have a lot of missing data, and how many patients you have. Sometimes even doing a meta-analysis, you can have access to the initial raw data; you can go to the initial investigators and ask for the initial raw data, and sometimes that will be effective. But if you have minimal data or it's really messy data, then you probably can't use it. So I think the quality of the data really is what matters here.

DR. EYDELMAN: So if I can just interject. Dr. Eydelman. Sorry.

If I can just interject. Part of the question is in light of your knowledge of the data, do you believe there is data currently that meets your criteria?

DR. KENNA: This is Marly.

You mean specific studies or just as a general concept?

DR. EYDELMAN: What I mean is do you believe that there is -- that the data -- that there is enough published data currently available that can be utilized given the criteria that you just delineated?

DR. KENNA: I think some of that has been discussed today. I think we have quite a lot of data both from inside the country and outside the country looking at children, actually all age candidates in the profound or even severe to profound range. Where we're clearly lacking data is in the single-sided deafness group, and perhaps, to a lesser degree, in the asymmetric hearing loss group. Especially in the asymmetric hearing loss group, it's not just the degree of hearing loss, it's how well they're doing with the hearing that they have. And I think those are the two areas that I think we've identified.

DR. NELSON: This is Peggy Nelson.

I'd also add that we don't have a lot of data on performance and noise in realistic situations and results of signal processing or whatever algorithms on that.

DR. HIRSCH: Barry Hirsch.

Can you just clarify because here the wording's a little bit different in that it says approval of device modifications as opposed to specifically saying software or programming strategies. Device. Is that meaning hardware?

DR. EYDELMAN: Device modification means anything. It can be software, it can be hardware. Any -- or even indication for use.

DR. HIRSCH: So, again, I would -- I'm sorry. Barry Hirsch.

I would again bring up the Hybrid. It's a device modification and --

DR. EYDELMAN: That's a different device.

DR. NANDKUMAR: I mean, it is. Yeah, it is a different PMA. We are not covering Hybrid at this panel meeting. Specifically cochlear implants, yeah.

DR. TOMBLIN: It seems as though this question has to do with the quality of the data, and I think I'm agreeing with you that it really -- I don't care where the data come from. Bad studies come from the U.S., and good studies come from outside the U.S., and retrospective studies can provide important insight, maybe sometimes better than prospective studies, if they're done well. So it seems to me as though all of these points are that knowing something is better than not knowing something, and the degree of confidence you can put in that comes from the quality of the study. So it seems to me as though I wouldn't want to say, you know, we'll only take a certain -- particularly when it's like only U.S. stuff. Sounds unnecessary, it seems to me, but you go for the best

information and the most information that you can, and it requires judgment.

DR. WOODSON: Dr. Houston.

DR. HOUSTON: Dr. Eydelman, so are you asking not only us to discuss the considerations for what constitutes reliable data and good research that we should trust, but also what our judgment is about particular topics or modifications that we've been discussing, whether there's enough data to support those?

DR. EYDELMAN: Yes.

DR. HOUSTON: Okay. So like, for example, the age at implantation issue, is that one of them or does than not count as a modification?

DR. NANDKUMAR: That's something the Panel proposed, so you --

DR. HOUSTON: Yeah, okay. So I'll say that I think that there is enough evidence now accumulated over the last almost 15 years to support lower -- or expanding the age at implantation to under 12 months.

DR. EYDELMAN: So just to reiterate. Since earlier we were having a discussion about the potential impact of this panel meeting of the future of ENT, one of the areas that could have tremendous impact is a clear delineation from this panel as to where good studies need to be done, and that's what I'm sort of trying to get verbally stated, what area? I don't mean who is going to sponsor it. I mean, what --

DR. HOUSTON: What, where, on what topic?

DR. EYDELMAN: Correct. Not meaning U.S. or OUS, meaning what subtopics need to be studied better, and that's what I was trying to --

DR. WOODSON: Dr. Madell.

DR. MADELL: Jane Madell.

I think that we have -- I think there is enough data. It's not a lot, but there is good data showing that the degree of hearing loss needs to change. I think that René reported a study, I have a study that I did a number of years back, other people have reported data. So I think we know we need to change criteria to allow better hearing. That said, I still think we could do more work in this area. I mean, we could use additional -- we know there are a lot of kids who have been implanted off label, and we need to look at their performance in a wider group of kids and see how they're doing and compare that to the kids who didn't get implanted.

DR. KENNA: There are two other groups that are sort of related that we really don't have a lot of really good prospective data on. One is in children -- Marly Kenna. I'm sorry.

One is in children who have other disabilities, because that's a very large portfolio now of our patients, and although we all know that they're a more challenging population, there isn't a lot of data about how they're challenging and really which children should we -- are there children we should never implant, for example? We don't really have good criteria for who the children are that we should really implant in that group of patients. I mean, they can be young and they could have great parents and they could still be very challenging, so I think that's a particular group. And then the flip side of that is we don't really have a validated measure for people who really are not good candidates and to support that. So they're sort of related.

DR. WOODSON: Dr. Tomblin.

DR. TOMBLIN: Yeah, Bruce Tomblin.

I would add to Dr. Madell's point that it seems as though -- this essentially pertains to that gray area we are talking about as we reduce the severity, that I think we do need more studies in there. There have been some. What seems to be lacking, I think, is studies where we're comparing children with similar hearing losses who have either hearing aids versus cochlear implants. Those studies kind of were done. I was thinking of Mary Joe Osberger's old work back in the '90s with the gold/silver/bronze, but we don't have much of that kind of work going on anymore. And yet, as we start to change our -- as that becomes an issue of where are the boundary points, it seems to me as though more work to kind of inform us. It may never clarify it, at least inform us of that. And when it seems as though it may be somewhat of a draw between a cochlear implant and a hearing aid might be needed. And hearing aids have changed considerably as well.

DR. CHANDRASEKHAR: Sujana Chandrasekhar.

I think we also need to know how we do in children whose home language is not English or Spanish, but something that maybe we don't have facility in. I think that's a big issue in the United States. It's also a big issue worldwide, where there are children traveling long distances away from their home language for implants and then going back to be immersed in a different language environment.

And then just looking at the options for data up here, I think we all -- I agree. Good data is very useful. There's an issue when you have unpublished data because it hasn't gone through peer review, and I think we know which journals we respect, we know the level of peer review that's there, and I think we would all opt for peer-reviewed publications versus unpublished data.

And then in (c), when you're looking at a data registry, again, if it's a biased data registry or you don't have access to the raw data that went into the registry, we may be getting data that's cherry picked. This is a place where I think we need collaboration between our societies and FDA to establish a registry that will be warts and all, that will tell us, you know, the kids who do well, the kids who do poorly, how many times the cords break, all of those things that really do affect their quality of hearing.

DR. MADELL: Jane Madell.

Another area that I think we haven't touched on at all on that, that I think has to be looked at, is the role of therapy methods and educational programming in determining how well a child does. It's something we sort of ignore, but we can't, because kids in different programs have all kinds of different exposures, and we need to look at that, and that needs to be looked at in some detail.

DR. HIRSCH: Barry Hirsch.

So the question there looks like it's just saying what data is good or not good, but you're asking what other areas we want to look at? What other topic?

DR. EYDELMAN: Well, it's a flip side of this. Right.

DR. HIRSCH: So another topic, to me, is auditory neuropathy. It hasn't really been addressed in any of this, and you're going to have kids coming in with, you know, medium thresholds around 60 dB and not doing anything with hearing aids; they're just doing very poorly with hearing aids. So I think that topic has to be addressed also, and I don't know how to propose it as a topic of study, but just make that on the list of things to look at.

DR. WOODSON: Dr. Tomblin.

DR. TOMBLIN: Yeah, I don't know that this is -- well, it could be a study area in and of itself, or it may need to be incorporated into other studies, and that is that I think we need to be more aware of how, perhaps, the child's hearing aid use -- that is, is it actually on the child and working and so forth, because we just make that assumption in our research that, well, they got fitted with a cochlear implant, that's no longer variable. But particularly with the young, with the infants and toddlers and so forth, that can be a considerable challenge for the parents. It can be -- some children will tolerate it more than others. So I think that's an area, I think, that needs to be addressed. And, in particular, I think, in some of our research, we need to include that variable because it might be part of the explanation for the poor performance.

DR. WOODSON: Dr. Ishiyama.

DR. ISHIYAMA: I think one of the areas that I briefly mentioned this morning is how accurately the newborn screening testing is done, and also once the hearing loss is identified, how are they followed because we see a lot of kids who are having difficulty getting in to be adequately evaluated. Delayed diagnosis. And that's a serious issue. And also once a child comes to us at a later age, some of the centers make an arbitrary cutoff and say once you're 3 years old, you're done. And I think that's not the case because I volunteered to go to a country, go to Armenia, some of the kids implanted -- a little bit older age with a very strong family support. They are completely aural.

So I think these are areas that still need to be explored because what the current -- diagnostic criteria for cochlear implant candidacy needs to be looked at in this regard because a lot of the state -- for example, California Children's Services directly use the FDA

guideline and they're using -- the guideline in place in California is really old. For example, it says that cochlear has to be completely normal in anatomy. So those are issues at a different -- level and needs to be looked at, what's been actually done in practice.

DR. WOODSON: Any other suggestions? Oh, okay. Ms. Scott and then Marly.

DR. SCOTT: I just wanted to -- Dr. Cherise Scott.

I just wanted to make a point around the data aspects. I would be hesitant to just dismiss data outside of the U.S. I think, one, it can be published; it may not be published in the U.S., but it could be published, so I would make that correction. And then, two, I think it should just meet specific criteria. I wouldn't dismiss data sources because even published data within the U.S. has biases, you know, and there can be some issues around that and that's been -- and there have been studies showing that even peer reviewed journal articles, there can be specific biases around that. So I would just kind of take each data source and put it against specific criteria and standards to make sure that, you know, whether you're using it correctly or not.

DR. EYDELMAN: So just to clarify, PMAs can be approved solely on data from outside of the U.S., so it can. And there have been approvals. But the applicant has to make the case that the data is appropriate for U.S. population, and I think, with cochlear implants, that's a specifically unique question.

DR. WOODSON: Marly.

DR. KENNA: Marly Kenna.

Just one other thing. Someone, one of the slides earlier on, showed a patient with a brain stem implant looking really pretty good, so I think one of the things that will come up

in the future is whether a patient is an appropriate candidate for an implant, a cochlear implant, versus an ABI. So that's sort of out there on the radar screen, but I think it is something in terms of candidacy that we will need to consider.

DR. WOODSON: Is that adequate for you?

DR. EYDELMAN: Yes. Thank you very much.

DR. WOODSON: All right. Let's go on to Question No. 4: If FDA determined that it is appropriate for clinical data from older children and/or adult patients to support premarket approvals for pediatric patients, particularly those younger than 6 years of age, post-approval studies may be required in some cases to confirm device safety and effectiveness in this patient population, as well as to inform future labeling. Please comment on the following:

a. Age-appropriate test metrics for children implanted at different ages (broken down into different age groups, e.g., 12-24 months, 3-6 years, 6-12 years, age 12 and above, etc.), to determine device effectiveness. What are the outcome domains (e.g., speech recognition in quiet and/or in noise, spoken language development, quality of life, etc.) that you would recommend as essential in a PAS?

So we did hear from, particularly from the guest lecturers, some of the testing that's used in younger children. Let's start with Jane. What would you recommend as essential tests or the ideal tests?

DR. MADELL: Jane Madell.

I would look at aided implant thresholds in each ear separately. I would look at speech perception as soon as the child can do it, which will vary. At normal conversation

and soft conversation in quiet and at least at normal conversation in competing noise. I would look at language development and auditory skill development to see that the child is -- whether to confirm whether the child is making 1 year's progress in 1 year's time or 3 months' progress in 3 months' time, depending on how often we evaluate the child.

DR. WOODSON: All right. Dr. Nelson.

DR. NELSON: Thank you. Peggy Nelson.

I think we have a couple of great models that we've seen today from published research on studies of functional daily life, studies of interactions with families, so I'd just add a couple of those. But I think from prelingual to sophisticated language use in noisy situations are appropriate.

DR. ISHIYAMA: Dr. Woodson? I'm sorry to interject.

DR. WOODSON: Yes.

DR. ISHIYAMA: Before we -- I would like to ask one more time to the guest speakers about the recommendation, especially in the age group from 12 to 24 months.

DR. WOODSON: Okay.

DR. ISHIYAMA: Dr. Hughes and Dr. Gifford.

DR. HUGHES: This is Michelle Hughes.

I guess what I'm wondering, in looking at this, is are you talking about chronological age here? Because I would think in terms of developmental age. Again, I'm sorry. I'm asking a question instead of answering one.

DR. WOODSON: Well, what would you recommend?

DR. HUGHES: I would recommend developmental age, for sure.

DR. EYDELMAN: Can I ask for clarification? How do you determine developmental age easily?

DR. MADELL: Can I suggest that we look at listening age?

DR. HUGHES: Well, but if we're implanting kids with multiple disabilities, then hearing age doesn't mean the same thing as it does in a child who is typically developing.

DR. WOODSON: Jane.

DR. MADELL: Jane Madell.

If we're implanting kids with developmental disabilities, the team should have a neuropsychologist or a pediatric -- developmental pediatrician on the team who can provide that information. You shouldn't be -- you should, excuse me. You shouldn't be implanting kids who have multiple issues if you do not have somebody who can help deal with that part of the child's development.

DR. CHANDRASEKHAR: Sujana Chandrasekhar.

So I think one -- since, from Question 1, the lower age should be 9 months and not 12 months. We heard about chronological age, we heard about post-implant age, we know about intellectual age, so I think there has to be some verbiage that FDA can put in that says the appropriate age measure given the milieu of the child. So if it's otherwise normal milestones, normal everything with hearing loss, that is a different age than a child with multiple disabilities with hearing loss.

DR. EYDELMAN: So would it be fair to say that we can talk about chronological age with a caveat, that if it differs from developmental age -- right. Because that's something I can imagine the language around.

DR. WOODSON: That makes sense to me.

DR. HIRSCH: Barry Hirsch.

Just also to add the prelingual and postlingual issues because they develop at different rates. And a small point, Sujana pointed this out, is that that age group that says 3 to 6 months should really be 2 to -- I'm sorry, 3 to 6 years should be 2 to 6 years.

UNIDENTIFIED SPEAKER: We're missing a whole year.

DR. EYDELMAN: Yes, we lost a year.

DR. WOODSON: If you're 2 to 3, you don't count.

(Laughter.)

DR. EYDELMAN: Okay. Thank you, Dr. Hirsch.

DR. WOODSON: Dr. Houston's light was on first.

DR. HOUSTON: All right. This brings up an important topic in our field that we don't currently have good standardized direct measures of language in 12- to 24-month olds. We use parental reports, and that's a challenge for our field right now to be able to develop measures that will track progress directly from the child rather than relying on parental reports. So we're kind of stuck right now with what we have, parental reports up until 24 months except for, you know, obviously -- to audiograms. And then, you know, once kids are old enough to do the tasks that require following instructions, then there are tons that you can use.

And I would recommend that in order to really see what the benefits are of cochlear implantation, that we look at a variety of measures, psychosocial and a lot of things that have been brought up. But even within the domain of language, there aren't that many

studies out there that look separately at, you know, lexical access, grammar development, vocabulary. A lot of the studies only look at -- use these omnibus measures of receptive and expressive language, and I think it's important to look at language a little more detailed than that.

DR. WOODSON: Would it be safe to say you're recommending we need to develop more tests?

DR. HOUSTON: Well, especially for -- well, for --

DR. WOODSON: For that age group.

DR. HOUSTON: -- the young age group. There are tests for the older age groups that get at more precise skills that are not being used.

DR. WOODSON: Dr. Tomblin.

DR. TOMBLIN: I guess I'd add to the list that we should -- at least, from my experience in both cochlear implanted children and children with hearing aid users, one of the early leading edges in terms of their benefit from those devices seems to be speech sound production. I think it can have problems, as Dr. Eisenberg mentioned, that there are other factors that can cause speech sound problems, but it does seem to be one of those things that seems to show the effect earlier, and then as we go on out, we start to see the language effects kicking in more. So I'd add measures of speech sound production.

DR. BRIETZKE: Just a quick -- also for quality of life. That is oftentimes why patients come in, and not only the child but of the caregivers as well. Really, an important outcome, maybe the most important one to look at.

DR. NORTON: Susan Norton.

We are looking at fairly simplistic measures of language development, as Dr. Houston said. I would argue that we need to look at higher levels of language function and use of language and academic development, particularly reading, since that is one of the stated goals of early ID, early intervention. And early implantation is better literacy.

DR. WOODSON: Any other specific recommendations for testing in the younger age group? I guess you're speaking there to testing long term to see how the language develops having been implanted early on.

Is that adequate, Dr. Eydelman? Okay.

All right. Children implanted at a relatively young age may require a longer term follow-up period than those implanted at a relatively older age. What would be the follow-up period that you consider appropriate for the pediatric cochlear implant recipients (e.g., younger than 6 years of age) in a post-approval study?

DR. CHANDRASEKHAR: Sujana Chandrasekhar.

Four to six years.

DR. WOODSON: Any other nominations? Yes.

DR. BRIETZKE: Scott Brietzke.

Took to heart one of the comments of one our industry speakers, I don't remember which one, is that the technology advances, and by the time the study was done, the device was already obsolete. So this is kind of like in the real world and a perfect world. In a perfect world, yes, we'd have big, long, nice follow-ups to give us all the data we want. In the real world, probably not practical, so probably some sort of balance is necessary.

DR. WOODSON: A balance, meaning what?

DR. BRIETZKE: I think some of the experts mentioned 1 to 2 years. Seems to be a reasonable approach to start with, but --

DR. WOODSON: Dr. Houston.

DR. HOUSTON: It depends what the question is, I guess. In order to answer what? In order to answer whether or not the modification that we're talking about is safe and effective?

DR. WOODSON: Yes.

DR. HOUSTON: If it's to answer that question, then we don't -- I mean, I think even in a fairly young population, even if they get the implant at 9 months, I think, you know, 3 years of follow-up is going to be able to tell you whether or not the device is safe and effective.

DR. EYDELMAN: If I can just clarify. Unfortunately, we never have 100% satisfaction that something is safe and efficacious. It's something that provides reasonable assurance of safety and effectiveness. So that's the bar that we're trying to get to.

DR. HOUSTON: Yeah. And that's why I said 3 years because I'm just imagining a child getting an implant before 12 months and maybe even -- you might even need 3 years, but at least up to the age where you can get a good PPVT so you know what their vocabulary is, because once you know what their vocabulary is, then that predicts all kinds of things down the line.

DR. WOODSON: Dr. Nelson.

DR. NELSON: Peggy Nelson.

But, again, I think there are some milestones that we can look at, so I don't think we

need to wait 3 years for some milestones that say this is working better than not having this work, so you know, we were talking about month-to-month changes, we were talking about changes in auditory behavior, changes in orientation towards sound, things like that. So I think there are some short-term milestones that could be developed that would say, oh, okay, things are going all right. And now we're going to watch for vocabulary growth a couple of years down the road.

DR. NANDKUMAR: I just wanted a quick clarification here. You mentioned the questions we would be asking in this kind of post-approval -- sort of keep in mind here that the kind of changes what we're talking here is that we have some assurance of safety and effectiveness, a reasonable assurance of safety and effectiveness from adult data and maybe older children, and what we're looking here -- the question we are asking is what about prelingual or the youngest children, right? That will be the direction of this post-approval study. And the PAS is now providing us things like a confirmation of that safety and effectiveness that we saw in adults and older children. Plus it's also going to give us some more information on appropriate labeling. For example, we talked about if we premarket approve these for the youngest, maybe it goes out there and it's up to the audiologists and so on. So in a post-approval study, for example, that labeling, that training or labeling or instructions for the audiologists would get refined, and perhaps there will be some precautionary language or certain direction that can -- better direction that can be provided so that even the newer audiologists could do the right thing if -- to certain situations. That's the kind of information that we will be looking for in that PAS. So given that -- now, that gives a perspective on how long the follow-up should be, to provide that

kind of information.

DR. WOODSON: So this is Dr. Woodson.

As I recall from the one post-approval study that was done, it was supposed to be a 1-year study, and it took them 4 years to collect the data. So if we say 3 years, I mean, is that going to be 9 years? I don't know.

Jane.

DR. MADELL: How long would -- for an adult, how long does the FDA require before you say the device is safe?

DR. NANDKUMAR: Typically, 1 year.

DR. MADELL: Well, then, 1 year for little kids.

DR. WOODSON: Sujana.

DR. CHANDRASEKHAR: Sujana Chandrasekhar.

The problem is that the data shows that these kids can take a long time to ramp up and --

DR. MADELL: But we're only talking about safety.

DR. CHANDRASEKHAR: No, no. We're talking about safety --

DR. NANDKUMAR: No, no.

DR. CHANDRASEKHAR: -- and efficacy.

DR. NANDKUMAR: The question --

DR. MADELL: Oh, okay.

DR. CHANDRASEKHAR: So the question is we're taking these -- the data we have in adults, we're extrapolating it to the small children, and we are hopefully looking for an

equivalent efficacy. That equivalent efficacy unfortunately may not manifest in 50% of the kids or 40% of the kids until 3 or 4 years post-implantation. So I think it has to be a longer term follow-up.

DR. WOODSON: So this is Dr. Woodson.

Are you talking about -- are you really going to where you're trying to prove equivalent effectiveness, or are you just trying to prove that it is effective and it's better than the hearing aids?

DR. EYDELMAN: You're trying to prove reasonable assurance of effectiveness. I mean, it's a PMA, so each device stands on its own. You're not comparing it to a hearing aid. You're trying to compare that it is an efficacious device for implantation in that patient population.

DR. KENNA: Marly Kenna.

I think we're assuming that over the age of 6 means that they are postlingually deafened and they have a progressive hearing loss and that the younger children are prelingually deafened or have a congenital hearing loss. But there are kids getting implanted who are definitely prelingually deafened at the age of 6 or 8. So I think once you start to do these types of studies, one of the things you have to take into consideration is exactly that because a postlingually deaf and a prelingually deafened 7-year-old needs to be followed for a long period of time and maybe much longer than a 2-year-old or a 1-year-old who may ramp right up.

DR. HOUSTON: Derek Houston.

I guess I feel like the question has kind of shifted back and forth a little bit from what

-- the duration needed to have reasonable assurance that it's safe and efficacious, but then there's also the question of what would be helpful for the audiologist and informative for the audiologist, so those are very different questions because you would want a longer -- you'd want as much information as you could get to inform providers.

DR. NANDKUMAR: I think the question -- I mean, this question was asked -- typically, what we do in post-approval studies is to look at long-term safety, confirmation of effectiveness if it's a different population, and any labeling modifications based on the study results.

DR. EYDELMAN: Let me try to clarify. What you're trying to show is that the device is safe and efficacious for that patient population. Now, once you figure that out, you will then take the outcomes and put it in the labeling, and that data will be used for educating or information of the audiologist. So that's a secondary benefit. That's not --

DR. HOUSTON: I guess I would say that for the secondary -- this is Derek Houston.

For the secondary benefits, you could get more benefits the longer you have --

DR. EYDELMAN: Right. But we're trying to be least burdensome.

DR. HOUSTON: Oh, okay.

DR. WOODSON: Dr. Scott.

DR. SCOTT: Cherise Scott.

I just wanted to follow up on what Dr. Nelson was talking about, this idea of kind of milestones or interim time points, because I'm wondering if the FDA would consider making that requirement of a longer follow-up, but with the idea of revising the labeling at specific time points given the amount of evidence at those points. So I don't know if that would be,

instead of waiting 3 or 4 years to revise a label for certain things, for example, kind of the burdensome idea that the person was presenting earlier around having a 12-month follow-up but then taking 4 years to change the label. So I'm just wondering if there's a way to kind of strike a balance.

DR. EYDELMAN: Okay. So a couple of concepts getting confused. Again, just want to try to clarify. The way the post-approval study requirements work, the study needs to be completed and then submitted to FDA. FDA analyzes it and, depending on the outcomes, we then update the labeling. It's not the continuous progress. It's not like, you know, we're going to be doing this every 3 months because, as you can imagine, we need to have a completed cohort to make conclusions. Now, for 1-year studies, the follow-up is 1 year. How long or how efficient the sponsor is in recruiting, and conduct of their clinical trial, depends on the sponsor. So I don't want to, in light of one sponsor's comments, I don't want the Panel to assume that every 1-year post-approval study ends up taking 4 years. That was the experience of that one particular sponsor in that one particular study.

So was that --

DR. WOODSON: Dr. von Jako.

DR. VON JAKO: Thank you. Ron von Jako.

So if I'm understanding correctly, if it's 1 year to do a study, it may take the manufacturer 1 year to set up the study. On the other end, too, if it's being stretched out to 4 or 5 years, the manufacturer may have made innovations and so forth, and technology moving forward and progress in which the data that they're collecting and the labels that it would affect may be different, or some of the information they may have might be useful

that they collected for, for a future product that's coming out to market, and some of it may not be. So then it's just a question of how practical is it for them.

Just wanted to put that out.

DR. WOODSON: Dr. Tomblin and then Dr. Madell.

DR. TOMBLIN: Bruce Tomblin.

It sounds like right now we really don't know how to do this. But it does seem as though it's a perfectly answerable empirical question. You just need the right kind of data. And, in fact, we probably even have the data out there, for instance, the CDaCI data, any longitudinal sample. If we think that 3 years could provide us with enough, then we could ask ourselves, particularly if we got a good enough array of data, to say can we go back and get to the data that Peggy was talking about, to say within 1 year are there indicators that, in fact, are good predictors of the 3-year outcome, and if so, then we'll have confidence in those. Right now, I don't think we, the community, has asked that kind of question that much. Are there early predictors of later outcomes that we can have confidence in? They're all sitting in people's data. Has CDaCI looked at that question?

Oh, then here we go.

DR. EISENBERG: Yeah, we usually look at it in every paper because we have a lot of baseline data, so -- this is Laurie Eisenberg.

So a lot of the analyses will look to see are there baseline characteristics that are predicting performance at later times and -- you know, like expressive language, functional hearing, pre-implant with hearing aids, so they're already performing well. The speech recognition hierarchy, even before they get an implant, they're already a little bit higher up

on the scale because they're benefiting from their hearing aid, they may be a little bit older, have some residual hearing and develop some language. So expressive language turned out to be sort of an important factor for those children that were in the top 10 percentile going through the speech recognition hierarchy.

Another factor that seems to show up a lot in almost every study is maternal sensitivity, and people are using that metric as a scale, you know, you can actually sort of make a judgment about maternal sensitivity. And we've been finding that that's been an important predictor variable that's not exactly clear why yet.

DR. TOMBLIN: Can I follow up? You were saying these are baseline. Are these pre-implant? What I'm --

DR. EISENBERG: Yeah.

DR. TOMBLIN: -- thinking of more, is --

DR. EISENBERG: Yeah.

DR. TOMBLIN: -- data that we're tracking with children post-implant.

DR. EISENBERG: Right.

DR. TOMBLIN: And ideally during that first year, let's say.

DR. EISENBERG: Right.

DR. TOMBLIN: Your follow-up was not that --

DR. EISENBERG: Yeah. We're actually -- we are doing it. We're in the middle of doing it now to get ready for the ACI abstract solution with -- so we would like -- we're trying to present 8-year data on the speech recognition hierarchy, and we're using survival analysis and Cox regression analysis to try and look at the predictor variables. And we're

also looking at the normal hearing trajectories just to validate the hierarchy. And I don't know, it looks like there may be different predictor variables based on where you are on the hierarchy and how long it takes you to get to a milestone. So I don't know, I can't give you the answer quite yet.

DR. WOODSON: Peggy and then Derek.

DR. NELSON: Peggy Nelson.

So, Dr. Eisenberg, don't leave. But would you say, not necessarily looking at one predictor or a couple, that within a year post-implantation the trajectory can be observed? Would you say that's a reasonable -- based on your longitudinal data, that it's a reasonable amount of time to estimate that there is a change in trajectory or not?

DR. EISENBERG: Well, certainly the *JAMA* paper, you know, looked at 3-year data, the ToBI data looked out to 6 years, and we are looking at growth rates, four different language metrics, different constructs of language or underlying abilities of language, the speech recognition hierarchy. We could look at data at 1-year, 2-year, 3-year, and it just depends. You've got a broad range in performance, and so it just depends where you would want a child to fall. At 1 year, would you want your child still to be at detection? I don't think that's a good sign of eventual outcome with the cochlear implant. If you have a child that is at 1 year getting into closed-set word identification, I think that child is doing pretty well, unless -- the top 10% by 1 year was already crossing into open-set word recognition, so it has to do with the distribution. And, personally, I think if at 1 year you're just at detection and maybe early pattern perception on the ESP, I'm not clear that that's going to be a good predictor for success.

And, Jane, you might speak to that, as well, with your experience.

DR. MADELL: Jane Madell.

I agree with you. I think -- I mean, the goal is always 1 year's progress and 1 year's time compared to typically developing kids. So if we are looking at a child and 1 year out they have not made 1 year's progress or not close to 1 year's progress, that is not a good indication that they're going to be able to do well. And so we need to know why they have not made progress. Are they wearing the device? Are their parents talking to them? Are they in a therapy program that's requiring that they use audition? There are a lot of factors that are involved in determining whether a child is successful.

DR. EISENBERG: And I think with speech recognition or the speech recognition hierarchy, when you look at the normal control group, I mean speech recognition tests are developed to be -- children with normal hearing should be at ceiling on those tests. If they administer the test at the age appropriateness of the test and they have the skills to do the tests -- so in other words, with an early ESP test, the low verbal ESP, can they cognitively make a difference between two choices? They may hear it, but cognitively they can't perform the test. So you've got capacity and you've got response and performance. And so you have to ferret out those issues with a very young child. So, you know, a child that's 3 years old may already be performing at ceiling on low verbal ESP, and once you get to the Pediatric Speech Intelligibility test by 3 and 4, should be at ceiling and quiet.

Children with a cochlear implant, I would not expect that level of growth unless they are in the higher levels of performance of the distribution, but certainly, I think, with our experience, again, by 5 years the vast majority of children are into open-set. But we don't

want -- you know, if you don't want to look at a child over 5 years, you get a lot of information at 1 year and 2 years, and again, if you're not progressing beyond detection, you need to look a little bit deeper about why that child hasn't shown any speech -- any growth in auditory capacity.

DR. MADELL: Jane Madell.

I'm not just talking about speech perception. We're also talking about language.

DR. EISENBERG: Definitely language. That's every center's --

DR. MADELL: Expect them to make 1 year --

DR. EISENBERG: Yeah. Sorry.

DR. MADELL: One year.

DR. EISENBERG: Yeah. That's every --

DR. MADELL: Derek is raising his hand.

DR. EISENBERG: That's every center's criterion of success is, you know, 1 year growth in 1 year.

DR. WOODSON: So Derek.

DR. HOUSTON: Derek Houston.

Children implanted -- among children implanted under 2 years of age, at 1-year post-implantation, the ability to learn novel words predicts later vocabulary. Houston et al. 2012, *Developmental Science*, r = 0.71, I think.

DR. WOODSON: Great.

Dr. Hirsch.

DR. HIRSCH: This question is addressing people 6 and under, so I assume that

encompasses a lot of prelingual kids. And is that trajectory different than kids who are perilingual at 2 and 3? I would think yes, and that would take longer than a 1-year curve to predict, I would think, that they would probably be closer to 3 years. So your experience in that would really help to understand this. So the question: To prelingual kids, how long does it take to get a good assessment of how they're going to do or are doing?

DR. EISENBERG: Pre-implant?

DR. HIRSCH: I'm sorry, Barry Hirsch.

This is post-implant studies, post-approval studies, how many years will it take for a kid who is prelingual to assess how he or she is doing?

DR. EISENBERG: I don't think you can just make one determination. Again, this is a population characterized by wide variability, and by far, the majority of children today are prelingual, actually, congenitally impaired. The children that may have progressive hearing loss, they have a leg up; by the time they lose their hearing, they've already developed some language. So I don't think you can just say, you know, how long will it take for a prelingually deaf child to show progress just because of the broad distribution in the population.

DR. HIRSCH: Barry Hirsch again.

That's the question. Is 1 year too short a time to assess, and is 3 years reasonable? Five years would be great, but it's such a burden on everybody.

DR. EISENBERG: Yeah.

DR. WOODSON: I'm going to take the Chair prerogative for a moment here because the question is, what's the least burdensome to make sure that it is -- that you have

reasonable assurance that it's safe and efficacious. We'd all like to know the answer to -- so you could tell the parents long-term what to expect. But if you want to know if the implant is working, that they're actually hearing through it, what are you going to learn in 3 to 5 years that you don't learn in 1 year?

DR. EISENBERG: I'm just going to say, based on our clinical population and working with our clinical audiologists, you'll learn a lot by 1 year in most of the children, wouldn't you say, Susan?

DR. NORTON: Yes, I would agree.

DR. EISENBERG: Usually you'll see some growth in 1 year beyond just detection and -- yeah.

DR. NORTON: Susan Norton.

Laurie, so you say there's this wide distribution of performance in your data, and we all see it clinically, and we have to ask are there characteristics of those children that do not make progress, who are below the 50th percentile, where these should be contraindications for implantation because the cost benefit is not there?

DR. EISENBERG: Somebody brought up the issue of who is a cochlear implant candidate, who is an ABI candidate. We're wrestling with that right now because, you know, we're looking at children who have a cochlear implant first, did not show any progress with it, and then we determined whether they would be an ABI candidate, and there are other reasons besides just not benefiting from a cochlear implant obviously. Originally, we thought what is the point of putting a child through two surgeries just because NIH is requiring this of our study, so a child who -- MRI shows absence of cochlear

nerve or a very iffy cochlear nerve, put the child at 1 year through a surgery just to know they may be wearing a device, getting nothing from it, waiting another year to go get brain surgery essentially.

Well, guess what? Some of those children are showing progress with the cochlear implant. We have actually rejected -- just this year rejected a child with cochlear nerve deficiency who did have a cochlear implant, and the child was detecting, was showing pattern perception within 6 months. And this is a child where it was probably on the fast track for an auditory brain stem implant. So we're now rethinking and revising our thinking about what could a child, even with really poor anatomy, can they do with a cochlear implant.

DR. WOODSON: I'd like to, right now, kind of call the question, and I want a show of hands for 1 year versus 3 years. How many people vote for 1 year?

(Count.)

DR. WOODSON: One, two, three, four, five, six.

How many vote for 3 years?

(Count.)

DR. WOODSON: One, two, three, four, five -- so that's your information.

(Laughter.)

DR. WOODSON: Thank you. Okay, (c). No, is it worth -- all right.

So now we are getting down to the last bite, yeah. To confirm safety and effectiveness in a post-approval study, patient factors (e.g., developmental and cognitive factors, and pre- and postlingual onset of severe-to-profound deafness) should be included

in the study design considerations. Please recommend any additional patient or device factors specific to the younger pediatric population that should also be considered in designing a post-approval study to support a premarket to postmarket shift in data requirements.

So what are some factors that you need to look for?

DR. KENNA: I think, as mentioned, the cause of the hearing loss. Is it genetic, is it structural, is it anatomic?

DR. NELSON: Peggy Nelson.

And then was there exposure to hearing, was it progressive, what's the degree of hearing loss in either ear? So how much hearing exposure, in general.

DR. WOODSON: Jane.

DR. MADELL: Jane Madell.

And also what kind of therapy did the child have? Is the child wearing the hearing aid, what kind of educational program -- the implant. What kind of educational program is the child in?

DR. WOODSON: Let's see. Susan.

DR. NORTON: Everything that's been said, but I would also ask for radiological verification of the placement of the device.

DR. WOODSON: Okay.

DR. ISHIYAMA: I think we may have a little time to -- but just for clarification, when a child has severe to profound sensory hearing loss not make any progress with the use of hearing aids, I think these -- I see no reason -- when a child also has some residual hearing

in the low frequencies, I see no problem proceeding with, for example, a cochlear 422 electrode, and if you could demonstrate that the hearing is preserved in low frequencies, I think -- I see no problem for them to use even the Hybrid processors. I wouldn't do the L24 in those kids at this point, but I see no problems doing a 422.

DR. WOODSON: Scott. Any other factors to include in a study?

DR. BRIETZKE: I would only spot the radiologic comment. I mean, oftentimes you can confirm placement with audiologic testing and -- if it's CT scans, radiation exposure to children, there's sedation involved, there's a lot of factors. I think you could maybe skip that stuff otherwise --

DR. WOODSON: So you might reserve that for patients where there's a question?

DR. BRIETZKE: There's a question, sure.

DR. WOODSON: Dr. Tomblin.

DR. TOMBLIN: I don't think I have -- I did bring up one time -- maybe I could put it on the list again. Documentation of cochlear implant use as well.

DR. WOODSON: Um-hum, okay.

Dr. Houston.

DR. HOUSTON: Parental education, family environment.

DR. WOODSON: Sujana. No?

Okay. Well, before concluding the meeting, Dr. Eydelman, is that enough information on that last question?

DR. EYDELMAN: This is enough information on this question; however --

DR. WOODSON: Okay.

DR. EYDELMAN: -- my staff has been trying to succinctly summarize all of your recommendations, and it appears we missed one small part.

DR. WOODSON: Okay.

DR. EYDELMAN: So if I can just ask you -- sorry. One -- hold on. Question 1b(iv), so if you can project that. So, basically, I think we moved on to (c) without discussing the requirement to support premarket approval for bilateral cochlear implantation.

DR. WOODSON: Oh, we didn't have a long discussion on that, but it seemed when we went around the table, people were saying they were in favor of bilateral implant.

DR. NANDKUMAR: Yeah. So I just want to give a quick clarification here.

DR. WOODSON: Okay.

DR. NANDKUMAR: So the way all cochlear implants are approved today, they are indications for -- all three manufacturers are silent on unilateral or bilateral.

DR. WOODSON: Okay.

DR. NANDKUMAR: So we don't -- so at this point, nobody is claiming that two is better than one, so in order to do that and put it in the indication, they'll have to come in with data. So I guess the question here is if that happens in the future, an applicant comes in with that -- again, the question is based on adult and older children data or literature, data that is provided, can we shift to postmarket the youngest group for that indication for the bilateral, benefit from bilateral.

DR. WOODSON: I know that Dr. Ishiyama is pretty strongly in favor of bilateral implantation for the 90 dB babies, right?

DR. ISHIYAMA: Yes.

DR. WOODSON: Yes. You agree?

(Off microphone comment.)

DR. WOODSON: Yes, Susan.

DR. NORTON: I have a question. So all of the cochlear implant companies, some of their marketing brochures tout the benefits of binaural hearing, so can they do that if it's not approved?

DR. NANDKUMAR: It depends on the wording. If it's --

DR. NORTON: So it's all --

DR. NANDKUMAR: I mean --

DR. NORTON: It's all just wordsmithing? Because they really are --

DR. NANDKUMAR: Right, correct.

DR. NORTON: -- making the statement.

DR. EYDELMAN: Thank you for bringing it to our attention.

DR. NORTON: Bilateral is better.

DR. WOODSON: Jane.

DR. MADELL: I don't think -- I think the data on the benefit of binaural hearing is not debatable. There is an enormous amount of data. I mean, just take Ruth Litovsky by herself. She's got -- I mean, there's article and article and article and article. The question is whether it's binaural implants or bimodal, but binaural hearing is not the issue, I don't think.

DR. WOODSON: Meaning that binaural hearing is better than --

DR. MADELL: Than monaural. A cochlear implant with nothing on the other ear is

not as good as a cochlear implant with anything on the other ear.

DR. WOODSON: So what is the specific question you want us to answer?

DR. NANDKUMAR: Bilateral electrical stimulation, that's the question. So two cochlear implants is better than one cochlear implant. That's the claim -- that's still a claim that's not approved in the indication specifically, in today's --

DR. WOODSON: Even for adults?

DR. NANDKUMAR: That's right.

DR. WOODSON: Wow.

DR. NANDKUMAR: What I mean to say is that it's not stated in that way, but the indications are silent. Like, for example, the Hybrid cochlear implant, we specifically said in the indications unilateral only. So the cochlear implant adult indication doesn't say that, so implanting it bilaterally is not off label; you can implant it on label, but the claim that two electrical stimulation on both sides is better than one side electrical -- that hasn't been approved for the manufacturers --

DR. WOODSON: Dr. Houston.

DR. HOUSTON: Derek Houston.

Yes, I think that if there are data presented showing a benefit of bilateral implantation in adults and older children, that that could be used for younger children.

DR. MADELL: I agree.

DR. WOODSON: Does anyone disagree with that?

(No response.)

DR. WOODSON: Is that satisfactory?

DR. EYDELMAN: Terrific.

DR. WOODSON: All right. So I would like to really thank Dr. Ronald von Jako, our Industry Representative; Dr. Cherise Scott, our Consumer Representative; Dr. Susan Broyles, our Patient Representative, and I want to know if any of you would like to make any final comments? Okay.

DR. VON JAKO: I think it was terrific to listen to what the manufacturers had to say, especially the three lady clinical scientists; it was very helpful information. And I think that taking into consideration of the manufacturers getting together and providing some criteria that they could work together with, collaborate perhaps with the FDA on, on determining the pre- and postmarket patient selections and how they would segment those out and come up with some potential guidance, I think that would be probably useful.

And thank you.

DR. WOODSON: Thank you.

I'd like to thank the Panel for being here. I'd like to thank the FDA for all their hard work in preparing all this material for us and for the guest speakers.

And, Dr. Eydelman, do you have any final comments?

DR. EYDELMAN: I just want to say that I'm incredibly impressed with the depth of comments and the commitment that each of the Panel members has demonstrated during today's deliberations. Sincere thank you from all of us.

DR. WOODSON: So the May 1st, 2015 meeting of the Ear, Nose, and Throat Devices Panel is now adjourned.

(Whereupon, at 4:58 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

EAR, NOSE, AND THROAT DEVICES PANEL

May 1, 2015

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TOM BOWMAN

Official Reporter